



P7-CRF-166

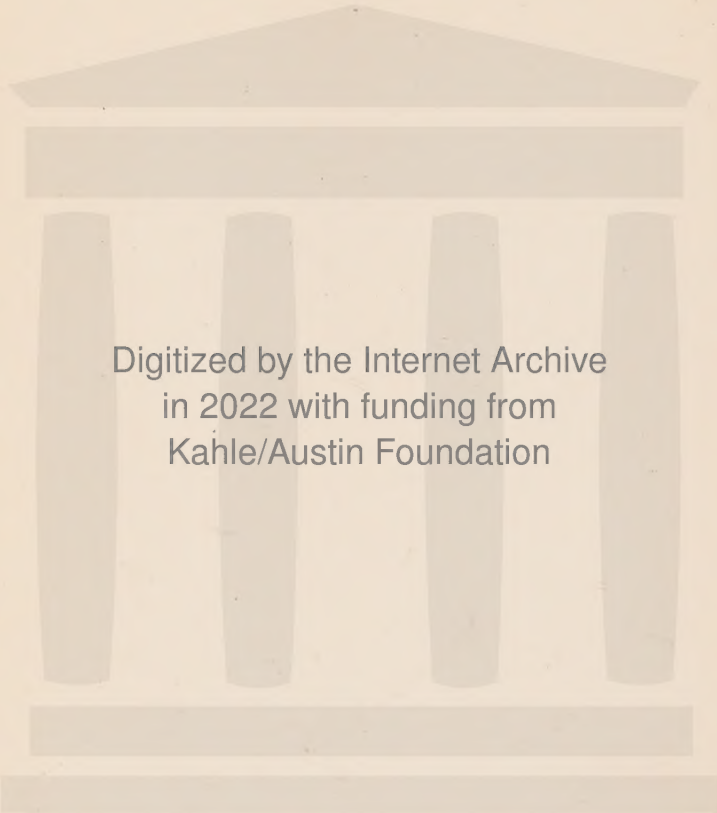


~~101~~

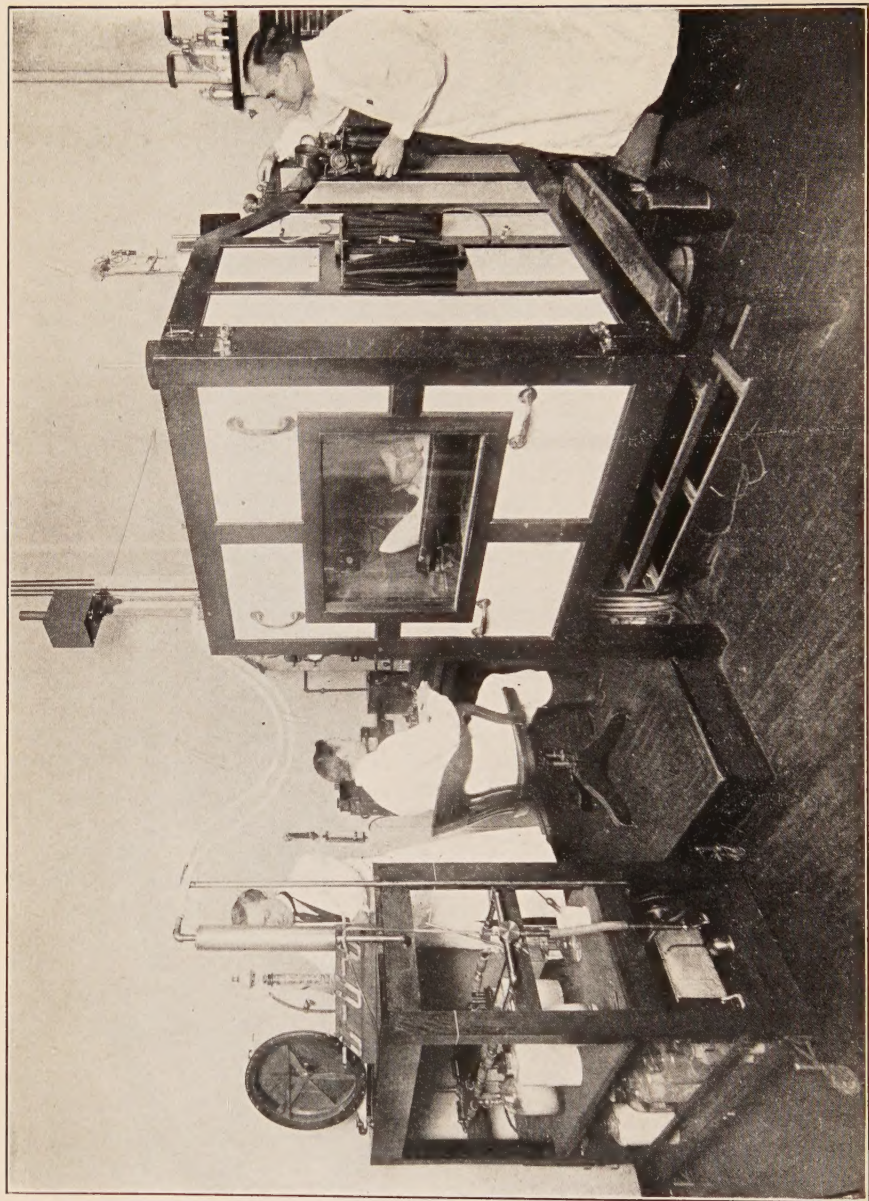
QP171

D72

Library



Digitized by the Internet Archive
in 2022 with funding from
Kahle/Austin Foundation



The Respiration Calorimeter of the Russell Sage Institute of Pathology.

BASAL METABOLISM IN HEALTH AND DISEASE

BY

EUGENE F. Du BOIS, M.D.

MEDICAL DIRECTOR, RUSSELL SAGE INSTITUTE OF PATHOLOGY; ASSOCIATE PROFESSOR OF
MEDICINE, CORNELL UNIVERSITY MEDICAL COLLEGE, NEW YORK

SECOND EDITION, THOROUGHLY REVISED

ILLUSTRATED WITH 92 ENGRAVINGS



LEA & FEBIGER
PHILADELPHIA
1927



QP191

.D72

COPYRIGHT
LEA & FEBIGER
1927

PRINTED IN U. S. A.

TO
GRAHAM LUSK

PUPIL OF

VOIT

PUPIL OF

LIEBIG

PUPIL OF

GAY-LUSSAC

PUPIL OF

BERTHOLLET AND LAPLACE

PUPILS OF

LAVOISIER

PREFACE TO THE SECOND EDITION.

THE subject of basal metabolism has during the last few years become of considerable importance to the practitioner of medicine. Most of the literature which deals with it, however, is written primarily for research workers or physiologists. The writer has, therefore, attempted to bring basal metabolism out of the realm of pure physiology into the domain of clinical medicine. This book is written for those engaged in the practice of medicine and surgery, for medical students, for physiologists and for dietitians. While it has not seemed necessary to give the details of the many instruments used for measuring the basal metabolism, the underlying principles of technic have been fully discussed.

No attempt has been made to compile a complete bibliography and the question of priority has received comparatively little attention. The recent literature has been cited much more often than the older publications. Animal experiments have scarcely been mentioned. I must, therefore, apologize to those great masters of the science of nutrition whose work has not been given due credit.

There has been a complete and thorough revision of the first edition. The chapters dealing with surface area and normal standards have been rewritten and rearranged in the light of the contributions of the last two years and the chapters on disease have received many additional references.

E. F. D. B.

NEW YORK, 1927.

CONTENTS

PART I. METABOLISM IN HEALTH.

CHAPTER I.

A BRIEF HISTORY OF THE STUDY OF THE RESPIRATORY METABOLISM	17
--	----

CHAPTER II.

CARBOHYDRATE, FAT AND PROTEIN	22
---	----

CHAPTER III.

A BRIEF REVIEW OF CERTAIN LAWS OF PHYSICS	53
---	----

CHAPTER IV.

THE GASES OF THE BODY	57
---------------------------------	----

CHAPTER V.

THE GENERAL PRINCIPLES OF RESPIRATION APPARATUS AND THE METHODS OF CALCULATION	67
---	----

CHAPTER VI.

THE ESTIMATION OF THE SURFACE AREA OF THE BODY	112
--	-----

CHAPTER VII.

FACTORS WHICH INFLUENCE THE NORMAL BASAL METABOLISM	128
---	-----

CHAPTER VIII.

THE SELECTION OF NORMAL STANDARDS	165
---	-----

CHAPTER IX.

THEORIES CONCERNING THE BASAL METABOLISM	186
--	-----

PART II. METABOLISM IN DISEASE.

CHAPTER X.

UNDERNUTRITION	207
--------------------------	-----

CHAPTER XI.

OVERNUTRITION AND OBESITY	228
-------------------------------------	-----

CHAPTER XII.

BASAL METABOLISM IN DIABETES	241
--	-----

CHAPTER XIII.

DISEASES OF THE THYROID	287
-----------------------------------	-----

CHAPTER XIV.

BASAL METABOLISM AND THE ADRENAL, PITUITARY AND SEX GLANDS	343
--	-----

CHAPTER XV.

BASAL METABOLISM IN DISEASES OF THE BLOOD	355
---	-----

CHAPTER XVI.

METABOLISM IN DISEASES OF THE HEART AND KIDNEYS	362
---	-----

CHAPTER XVII.

FEVER	368
-----------------	-----

CHAPTER XVIII.

THE WATER METABOLISM	398
--------------------------------	-----

CHAPTER XIX.

INFLUENCE OF THE DISEASES OF THE NERVOUS SYSTEM ON BASAL METABOLISM	406
--	-----

CHAPTER XX.

THE EFFECTS OF DRUGS UPON THE BASAL METABOLISM	412
--	-----

BASAL METABOLISM IN HEALTH AND DISEASE.

PART I.

METABOLISM IN HEALTH.

CHAPTER I.

A BRIEF HISTORY OF THE STUDY OF THE RESPIRATORY METABOLISM.

THERE are certain manifestations of the abnormal metabolism in disease which must have been evident to clinicians long before the introduction of modern methods of study. Such, for instance, are the loss of weight which accompanies diabetes and the increased skin temperature and wasting which are typical of fever. Even at a comparatively recent date Friedrich Müller¹ discovered the high metabolism of exophthalmic goiter by noting the large nitrogen losses in patients who were receiving enough food to maintain a normal person in nutritive balance.

Perhaps we should give more credit to those of our predecessors who were wise enough to be the first to state clearly facts which we now use in clinical medicine. Unfortunately these worthies also stated with equal clarity many things which were not facts. If 90 per cent of their statements were wrong a scientific worker could not make good use of the 10 per cent that were right. With the development of modern medicine there arose a generation of investigators who were correct or nearly correct in the majority of their statements as far as we can judge at the present time. These men also should be given their proper credit.

¹ Müller: *Deutsch. Arch. f. klin. Med.*, 1893, 51, 335.

Clinical medicine is indebted to a few physicians who have made important discoveries in the metabolism in disease and to a large number of chemists and physiologists who have laid the foundations of our knowledge of the metabolism in health. Graham Lusk¹ in his recent review of the history of metabolism and J. R. Murlin² in his excellent articles on the normal processes of energy metabolism have shown our indebtedness first to the English and French and then to the German schools. Lavoisier not only discovered the significance of oxygen in respiration but with the aid of Seguin developed an apparatus which measured with considerable accuracy the metabolism of man and demonstrated the basic facts regarding the increases in heat production caused by exposure to cold, by food and by exercise. This extraordinary pioneer with his combination of originality and clear thinking not only founded a science but established its most important facts. Such men are rare in history but we cannot help recalling the similar accomplishments of Laënnec and Pasteur, his countrymen.

From the technical standpoint we are still indebted to Regnault and Reiset³ who published in 1849 the description of a closed circuit apparatus for the measurement of the oxygen consumption and carbon dioxide production of animals. The subject of the experiment lay in a glass cage and the carbon dioxide was absorbed in an alkaline solution. As the animal used up oxygen this was supplied from glass containers. The general principles of this device are embodied in all the modern closed circuit apparatus. Regnault was not merely a technician but used his machine to study the relationship of oxygen and carbon dioxide, the respiratory quotient (R. Q.) and the manner in which this was affected by the various foodstuffs. He also noticed that sparrows absorbed more oxygen per unit of body weight than chickens and ascribed it to the fact that the smaller animals presented a relatively larger surface to the cooling effects of air.

Liebig made great contributions to our knowledge of the chemical processes within the animal body and divided the

¹ Lusk: *Endocrinology and Metabolism*, New York, Appleton & Co., 1922, 3, 3.

² Murlin: *Endocrinology and Metabolism*, New York, Appleton & Co., 1922, 3, 515. Murlin, *Abt's System of Pediatrics*, Philadelphia, W. B. Saunders Company, 1922, I.

³ Regnault and Reiset: *An. de chimie. et phys.*, Paris, 1849, 26, 299.

foodstuffs into proteins, fats and carbohydrates. He did, however, ascribe the metabolism of protein to muscular work and this error has persisted in the popular imagination even to our own day. At about the same period as Liebig and Regnault, two Germans, Bidder and Schmidt, working in Russia, developed a more exact method of calculating the metabolism from the respiratory exchanges and formulated the following clear conception of the basal metabolism: "For every species of animal there is a typical minimum of necessary metabolism which is apparent in experiments when no food is given."

A few years later Pettenkofer at the suggestion of Carl Voit built a respiration chamber large enough for the study of human subjects and these two, working in Munich established our modern conceptions of the metabolism of man. Rubner, a pupil of Voit's, carried the work much farther and built the first respiration calorimeter which proved that the food oxidized in the body gave off the same amount of heat as if it were burned outside the body. He was able to show that under similar physiological conditions warm-blooded animals of different sizes and different species gave off approximately the same amount of heat per unit of surface. Richet in France also enunciated this very law at almost exactly the same time. The first man who realized the importance of absolute muscular repose in determining the basal metabolism of human subjects was Nathan Zuntz who, with Geppert, constructed an apparatus of the open circuit type which was capable of measuring the oxygen consumption and carbon dioxide production in short periods just as accurately as any of the modern machines.

In America, important contributions to the normal metabolism have been made by Atwater and Benedict who used extremely accurate respiration calorimeters in which men could live and work for days at a time. Lusk with a smaller apparatus has devoted his attention chiefly to the effects of foods and the intermediary metabolism. He has used with great success human diabetes and phlorhizin diabetes as a key to the study of the processes which take place within the body. Clinicians are indebted to F. G. Benedict and his associates of the Nutrition Laboratory in Boston for the study of normal controls and for the development of apparatus suitable for use in hospitals.

At a very early date clinicians naturally began to study the gaseous exchanges in disease but the methods were so crude

and the normal processes so imperfectly studied that the results of this labor amounted to little.

Pettenkofer and Voit¹ soon after the construction of their respiration chamber saw the importance of studying diabetes and in 1867 made a series of experiments on a young man suffering from this disease. They also examined patients with anemia. Three years later Liebermeister² determined the carbon dioxide output of 2 malaria patients before, during and after a malarial chill and obtained a picture which has scarcely been modified by the work of the last fifty years. In 1891 Leo³ made a number of experiments on diabetics using the Zuntz-Geppert apparatus and these were followed in the next few years by a considerable number of important studies of different diseases by various investigators using this same machine. Chief among these was Kraus,⁴ who worked with cardiac patients, febrile subjects and others. Some of the technic at this period, however, was distinctly poor and it seemed necessary to invent all sorts of theories regarding the metabolism in disease in order to account for the abnormal respiratory quotients.

When Magnus-Levy entered this field about 1894 a new era began. He had mastered the Zuntz-Geppert technic and had developed experimental methods which were fully as good as those in use at the present time though perhaps more laborious. His contributions included a careful study of the effect of food on metabolism and also of age and sex, of pregnancy and of menstruation. He seems to have realized fully the importance of studying normal controls in order to determine the effects of disease. His greatest contribution was, of course, his demonstration of the increase of metabolism in exophthalmic goiter in 1895.⁵ This was followed by studies in myxedema, diabetes, anemia and other pathological condition. Very properly he made the most of his opportunities and skimmed the cream leaving little of importance for the workers of the next few decades.

There seems to have been a new wave of interest in metabolism in disease starting about 1908. Benedict at this time had just begun to use his new "unit" respiration apparatus and with Joslin was undertaking an extensive study of dia-

¹ Pettenkofer and Voit: *Ztschr. f. Biol.*, 1867, **3**, 380.

² Liebermeister: *Deutsch. Arch. f. klin. Med.*, 1871, **8**, 153.

³ Leo: *Ztschr. f. klin. Med.*, 1891, **19** (Sup. Heft), 101.

⁴ Kraus: *Ztschr. f. klin. Med.*, 1893, **22**, 449.

⁵ Magnus-Levy: *Berl. klin. Wchnschr.*, 1895, **32**, 650.

betes. In Germany, Grafe and Rolly began to study fever and other clinical conditions. In 1911, a Benedict unit apparatus was installed in Bellevue Hospital, New York, and two years later a respiration calorimeter was built there by the Russell Sage Institute of Pathology. This was under the directorship of Lusk who was at the same time conducting animal experiments in a similar calorimeter in the Cornell Medical College across the street. Work with this calorimeter in the medical wards emphasized the fact, already well known to Magnus-Levy, that the measurement of the basal metabolism was of great clinical service in the diagnosis and treatment of diseases of the thyroid gland. This was best demonstrated by Means in Boston and later by Boothby of the Mayo Clinic. Simple forms of apparatus were devised by Benedict and others and now there are several thousand such machines in use in the United States. We have reached the stage of quantity production and the literature is filled with studies of the basal metabolism. Fortunately many excellent reviews of the whole subject have been published in the last few years and the reader will find great profit in consulting the recent comprehensive articles of Grafe,¹ Boothby and Sandiford², McCann,³ King,⁴ Murlin,⁵ Benedict,⁶ Takahira⁷ and Talbot.⁸ The technic of this newer work is on the average rather better than that of the previous decades but one misses the personal touch of the older days when only those with a long and arduous training in metabolism were able to manipulate the difficult apparatus and interpret the results. We are reminded of the bow of Ulysses which could be strung only by the great Ithacan himself.

¹ Grafe: Die pathologische Physiologie des Gesamtstoff-und Kraftwechsels bei der Ernährung des Menschen, Munich, J. F. Bergmann, 1923; also published in *Ergebnisse der Physiologie*, 1923, 21², 1.

² Boothby, W. M. and Sandiford I.: A Laboratory Manual on the Technique of Basal Metabolic Rate Determinations, W. B. Saunders Company, Philadelphia, 1920; *Physiological Reviews*, 1924, 4, 69.

³ McCann, W. S.: *Calorimetry in Medicine*, Williams & Wilkins Co., Baltimore, 1924, also published in *Medicine*, 1924, 3, 1.

⁴ King, J. T., Jr.: *Basal Metabolism*, Williams & Wilkins Co., Baltimore, 1924.

⁵ Murlin, J. R.: *Abt's Pediatrics*, W. B. Saunders Company, Philadelphia, 1923, 1, 520.

⁶ Benedict, F. G.: *Methoden zur Bestimmung des Gaswechsels bei Tieren und Menschen*, Abderhalden's Handbuch der biologischen Arbeitsmethoden, Urban and Schwarzenberg, Berlin and Vienna, 1924, Abt 4, Teil 10.

⁷ Takahira, H.: Report of Metabolic Laboratory, Imperial Government Institute for Nutrition, Tokyo, 1925, 1, No. 1.

⁸ Talbot: *Physiological Reviews*, 1925, 5, 477; *Monatschr. f. Kinderheilk*, 1924, 27, 465.

CHAPTER II.

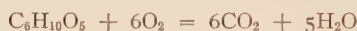
CARBOHYDRATE, FAT AND PROTEIN.

THE METABOLISM OF CARBOHYDRATES.

SINCE carbohydrates are the simplest of all foods it seems advisable to discuss their metabolism before proceeding to the fats and proteins. Not only are they the simplest but they are also the most important from the standpoint of the total energy furnished to the body.

Our chief foodstuff is starch, a polysaccharide with a formula which may be expressed as $(C_6H_{10}O_5)_x$. When ingested the saliva and pancreatic juice convert starch into soluble starch, then into dextrins, then maltose and then glucose, a monosaccharide with the formula of $C_6H_{12}O_6$. As such it is absorbed through the intestinal wall into the blood and after passing through a number of intermediate stages is oxidized in the cells forming carbon dioxide and water. In its oxidation it gives off all the potential heat which it, like any other fuel, contains.

We can express the reaction as follows:



If we calculate the molecular weights we obtain the following:

	Starch.		Oxygen.		Carbon dioxide.		Water.
C	$6 \times 12 = 72$			$6 \times 12 = 72$		
H	$10 \times 1 = 10$			$10 \times 1 = 10$
O	$5 \times 16 = 80$	$12 \times 16 = 192$		$12 \times 16 = 192$		$5 \times 16 = 80$	
	<hr/>			<hr/>		<hr/>	
	162	+	192	=	264	+	90

The factor required to convert grams of oxygen to liters is 0.6997 hence the oxygen consumed would be $192 \times 0.6997 = 134.34$ liters. The factor to convert grams of carbon dioxide to liters is 0.5089 hence 264 grams will consume 264×0.5089 or 134.34 liters. We note that the volume of carbon dioxide produced exactly equals the volume of oxygen consumed. This of course follows from the fact that 6 molecules of each

gas entered into the above reaction and 1 molecule of one gas occupies exactly the same space as 1 molecule of any other gas at a given temperature and pressure. Now the respiratory quotient (R. Q.) of a foodstuff is found by dividing the liters of carbon dioxide produced in the reaction by the liters of oxygen consumed. In the case of all carbohydrates this quotient is naturally 1.00. Carbohydrates contain in their molecules exactly enough oxygen to combine with their hydrogen and when they burn they require outside oxygen only for their carbon. We shall see later that fats and proteins require outside oxygen not only for carbon but also for some of their hydrogen.

To return to our calculations: We have seen from the molecular weights that 162 grams of starch + 192 grams of oxygen furnishes 264 grams of carbon dioxide + 90 grams of water. Since each gram of starch liberates 4.2 calories 162 grams of starch will provide 680.4 calories. We can therefore write the equation: When 680.4 calories are liberated from starch by combination with 234.34 liters of oxygen each liter of oxygen utilized represents 5.065 calories. This factor for the calorific value of a liter of oxygen corresponds closely with the factor of 5.047 obtained by Zuntz and Schumburg who employed slightly different values for some of the elements entering into the calculation. It may be noted at this point that most of the theoretical and practical calculations used in metabolism work may vary 0.5 of 1 per cent or more depending on the differences in physical constants given by various authorities. Fortunately such small differences are of no practical importance.

The simple calculation given above shows us how we may find the heat production of a man who is deriving practically all his energy from carbohydrate. We merely have to multiply the liters of oxygen consumed by the factor 5.047 to obtain the calories. Of course no man ever derives absolutely all his calories from carbohydrate but we shall see later how we can make the proper corrections. Fortunately the factors for protein and fat are not very different from those employed for carbohydrate.

One molecule of glucose, $C_6H_{12}O_6$, by combining with 6 molecules of oxygen produces 6 of carbon dioxide and 6 of water. The molecular weight is 180 which is greater than that of starch and the heat value is smaller being only 3.74 calories

per gram. The 180 grams of glucose will represent 673.2 calories and since 134.34 liters of oxygen will be consumed in the reaction, each liter will have a caloric value of about 5.011.

If we return to our chemical reactions we note that the oxidation of 162 grams of starch results in the formation of 90 grams of water. This means that every 100 grams of dry starch metabolized in the body forms 55.5 grams of water and a similar amount of glucose 60 grams of water. We shall return later to emphasize this important fact which has not yet impressed itself upon students of metabolism.

We have seen that starch burned in a calorimeter furnishes about 4.2 calories per gram, some authorities giving a slightly lower figure. Glucose furnishes 3.74 calories, sucrose about 3.96. Rubner has calculated the average proportions of these in our diet and has given us the figure of 4.1 as the average heat value of carbohydrate food. Since carbohydrates are almost completely absorbed by the intestine it is not necessary to make any subtraction for the loss in the feces.

Practically all investigators have followed Rubner's¹ figures for carbohydrate which have been confirmed by Atwater and others. Of course everyone subtracts the calories of glucose in the urine in cases of diabetes. We should also make allowances in any case where there is an unusual loss of carbohydrate in the stools either on account of some intestinal trouble or on account of rough, unabsorbable fruits or vegetables in the diet. It is not accurate to employ the factor 4.1 if the diet contains a large proportion of glucose. These differences do not bother us if we make respiration experiments because we now calculate the heat value of the carbohydrate actually oxidized from the oxygen used in the reaction.² The older method of calculating the metabolism by measuring the food intake and determining its caloric value over long periods of time has become almost obsolete.

When carbohydrate food is taken it is rapidly digested, and absorbed and in a subsequent chapter we shall see how quickly it begins to manifest itself in the respiratory metabolism. We must remember that carbohydrates ingested, even after a period of fasting, enter a body which contains a considerable amount of glucose in the blood and glycogen

¹ Rubner: *Ztschr. f. Biol.*, 1901, 42 (New Series 24), 261.

² Most investigators have disregarded the slight differences between the calorific values of oxygen for glucose and for starch.

in the liver. We are all now familiar with the usual range in blood sugar which averages about 0.1 per cent and if we consider the blood volume 5 liters this amounts to 5 grams of blood glucose in the body. To this we should add an unknown amount for the sugar in the other body fluids and in the muscle cells. The liver can store perhaps as much as 300 grams of glycogen and Schoendorf¹ has proved that the liver of dogs may contain 18.7 per cent of this carbohydrate

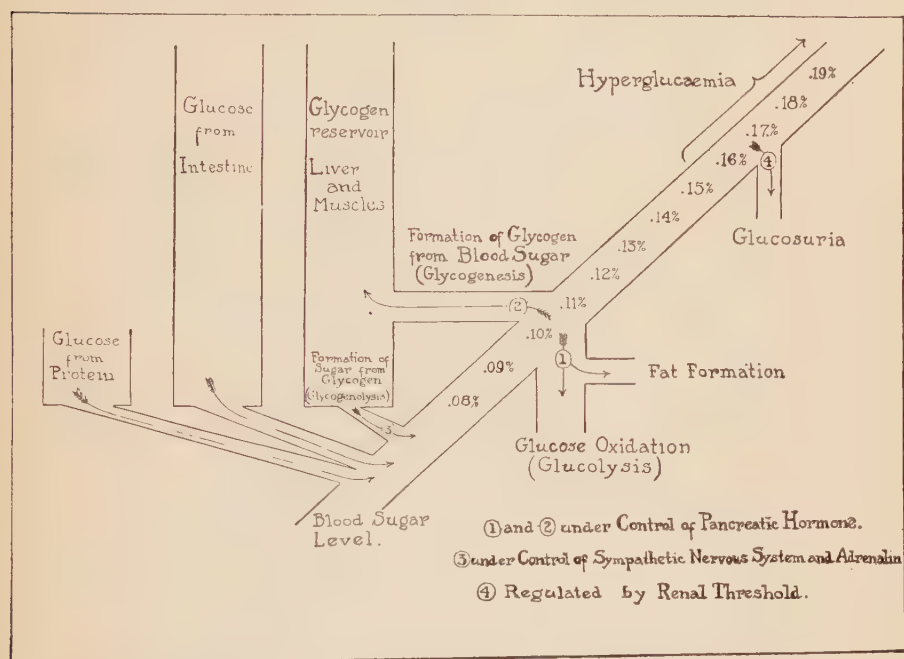


FIG. 1.—Schematic illustration of the factors which regulate the sugar concentration of the blood. (Ringer and Baumann.) (From *Endocrinology and Metabolism*, D. Appleton & Co.)

which is about equal to the amount contained in sweet corn or green peas. Observations on fasting men have shown that the body can utilize 93 to 232 grams of carbohydrate which have been stored away in glycogen depots.² Apparently these are not completely exhausted even after many weeks of starvation.

¹ Schoendorf: *Arch. f. d. ges. Physiol.*, 1903, 99, 191.

² Benedict: *Carnegie Institution of Washington Publication No. 77*, 1907, and *Publication No. 203*, 1915.

Ringer and Baumann¹ have drawn a diagram which shows clearly the factors which regulate the sugar concentration of the blood. They represent the blood as an inclined tube with some openings through which the glucose may enter and some through which it may leave the stream. Glucose enters the blood as it is absorbed from the intestine, as it is split off from the protein molecule and as it is mobilized from the glycogen depots in the liver and muscles. At the ordinary level of blood sugar the glucose leaves the circulation as it is oxidized or utilized for the formation of fat. Rising a little above this level it may be stored in the liver in the form of glycogen. Mounting still higher these three sources of loss may continue and even be augmented but finally the blood sugar may rise above the renal threshold and glycosuria will result. We should add to this diagram another small outlet since Stanley R. Benedict² has shown a normal excretion of carbohydrate amounting to about a gram a day.

The normal renal threshold varies in different individuals, but as a rule there is no spilling of sugar unless the blood glucose rises over 0.15 to 0.16 after a heavy meal of sugar. In diabetes the long continued hyperglycemia seems to raise the threshold, sometimes to extreme degrees. Nephritis raises the threshold for sugar just as it does for other substances.

In another place we shall deal with the somewhat complicated reactions when glucose is transformed into fat and discuss the formation of glucose from the glycerol of fat. The derivation of glucose from protein will be discussed when we come to the protein metabolism.

THE METABOLISM OF FATS.

It is difficult to arouse much interest in fats. They seem to be comparatively inert substances with long and complicated chemical formulæ. We do not know any too certainly the mechanism of their digestion, absorption and metabolism. Nevertheless they are extremely important since they furnish about a third of our calories in health and a much larger proportion in starvation and in diabetes. Recent work in diabetes

¹ Ringer and Baumann: *Endocrinology and Metabolism*, New York, Appleton & Co., 1923, 3, 252.

² Benedict, S. R., Osterberg and Neuwirth: *Jour. Biol. Chem.*, 1918, 34, 217-262.

has brought to light fascinating theories regarding the relationships of fats and carbohydrates. The normal fat metabolism has been reviewed by Bloor¹ in an authoritative manner. We may condense his statements into the following paragraph.

The lipoids have been divided into several groups but at the present time we are interested only in the so-called simple lipoids or fats. These are esters of the triatomic alcohol glycerol. Edible fats are usually mixtures of tristearin, tripalmitin and triolein, substances which differ considerably in their melting points but not very greatly in their chemical formulæ. When taken into the stomach they encounter there a lipase which may become a factor in digestion if the acidity is low and the emulsification sufficient to permit of good surface action. The presence of much fat in the stomach inhibits the secretion of acid and slows the passage of food into the intestine. Small amounts of fat or emulsions such as milk or oils may leave the stomach rather rapidly. Usually the fat passes the pylorus a little at a time and enters the intestine where it finds ideal conditions for its digestion. The pancreatic secretion contains large amounts of active lipase which is rendered even more active by the presence of bile. There is also a lipase secreted by the intestinal wall. The pancreatic juice, bile and intestinal secretions are alkaline, so the fatty acids formed by the hydrolysis of the fats unite with the alkalis to form soaps which in turn aid in the emulsion of the rest of the fat. The solubility of these fatty acids and soaps is increased by the bile which, indeed, seems to accelerate every stage of the process. It is probable that the fats are absorbed from the intestine in water-soluble form as fatty acids and soaps and are then resynthesized in the wall of the gut. This fat passes into the blood stream by way of the thoracic duct though perhaps some may find its way through other channels. In the blood the suspension of the minute particles causes a slight milkiness of the plasma which persists eight to fourteen hours after the fat meal. Under certain conditions and particularly in severe diabetes the lipemia may be very high. As a rule the fat is withdrawn from the blood and metabolized or stored in the tissues almost as rapidly as it is absorbed. The organism is usually able to deposit a fat which is characteristic of the species but if the

¹ Bloor: *Endocrinology and Metabolism*, New York, Appleton & Co., 1923, 3, 183.

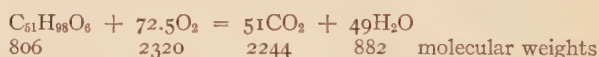
food contains large amounts of foreign fats these may find their way unchanged to the depots of the body.

Emulsified fats are almost completely absorbed by the intestines and as a rule the fats with low melting points are better assimilated than those which do not melt at body temperature. Even such fats as butter and bacon, which are easily absorbed in moderate quantity cannot be well taken care of in amounts over 300 grams a day. The following table will show some of the more important coefficients of absorption. We must remember that the intestine excretes fatty substances in small amounts even during starvation.

TABLE I.—FOOD ABSORPTION: NORMAL INDIVIDUALS.¹

Food.	Percentage loss.		
	Fat.	Carbohydrate.	Protein.
Roast beef	2.6
Hard-boiled eggs	4.4	...	2.6
Milk	5.2	0	7.1
Fine white bread	1.1	21.8
Rice	0.9	20.4
Potato	0.7	19.5
Mixed diet with:			
Bacon (99 gm. fat)	17.4	1.6	12.1
Bacon (195 gm. fat)	7.8	6.2	14.0
Butter (214 gm. fat)	2.7	6.2	11.3
Butter and bacon (350 gm. fat)	12.7	6.8	9.2

The oxidation of fat can be represented by taking as an example tripalmitin, $C_{51}H_{98}O_6$.



Since each gram of animal fat gives about 9.5 calories, 806 grams would furnish 7657 calories and would require in their oxidation 2320 grams of oxygen which equals 1623 liters. Therefore each liter of oxygen would have a calorific value of 4.72. Zuntz and Schumburg² using formulas which more nearly represent the average fats consumed in the body obtain the figure 4.686. As a matter of fact the caloric value of a liter of oxygen is almost the same when different food fats or human body fat are oxidized.

If we look once more at the formula for tripalmitin we are struck by the fact that it contains very little oxygen, not

¹ Rubner, Gruber and Ficker: Handb. der Hyg., Leipzig, 1911, I, 131.

² Zuntz and Schumburg: Phys. d. Menschen., Berlin, 1901.

nearly enough to oxidize all its hydrogen to say nothing of its carbon. For this reason the molecule of the fat requires from outside sources 72.5 molecules or volumes of oxygen and produces only 51 molecules or volumes of carbon dioxide.

The respiratory quotient (R. Q.) therefore is $\frac{51}{72.5} = 0.703$. The quotient for mixtures of fat used in most calculations is 0.707.

Fats are rich in hydrogen which furnishes a great deal of heat for a small weight and therefore fats have a large fuel value. They consume a correspondingly large amount of oxygen binding much of it with hydrogen to form water. We can see that 806 grams of tripalmitin will form 882 grams of water. In other words the body obtains more water from 100 grams of this solid fat than from 100 grams of water itself. To this we shall return later when we try to show clinicians some of the errors they have been making in their water-balance experiments.

Rubner adopted the figure of 9.3 as the average caloric value of the fats used in our food. Later analyses would indicate that the fats really have a heat value nearer 9.4 or 9.5, so that if we use Rubner's¹ factor, we are making a small allowance for the losses in the feces. Rubner distinctly states that his factors of 9.3 for fat and 4.1 for carbohydrate, were not intended to take account of the losses in the stools, which on an average diet with vegetables predominating amount to about 8 per cent of the original energy content. In the case of carbohydrates and fats the losses are so small that it does not make much difference in our calculations whether we subtract them or not. Atwater² reckons that there is a loss of 5 per cent of the animal fat and 10 per cent of the vegetable fat in the excreta so he proposes the average net value of 8.75 calories for each gram of fat ingested. Most investigators have followed Rubner, some have followed Atwater. The French have adopted a compromise figure 9. For clinicians it would seem best to retain the standard of 9.3 calories and deduct an appropriate amount if there are excessive losses of fat in the stools.

Experience in feeding cattle and pigs has clearly demon-

¹ Rubner: *Ztschr. f. Biol.*, 1901, 42 (New Series 24), 261.

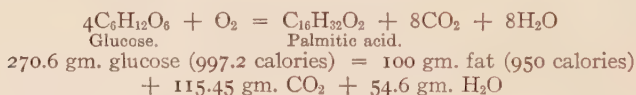
² Atwater and Bryant: Report of the Storrs (Conn.) Exper. Station, 1899, p. 73.

strated that fat can be formed from carbohydrates. When geese are stuffed with cereals in order to produce *pâté de foies gras* for the market this reaches an extreme grade. In man such fat formation takes place after large meals rich in carbohydrate especially during convalescence from wasting diseases.

If a substance rich in oxygen such as glucose is converted into a substance poor in oxygen such as fat it is obvious that only a small amount of oxygen will have to be absorbed from outside sources. This means that the respiratory quotient

$$\frac{\text{Vol. CO}_2 \text{ produced}}{\text{Vol. O}_2 \text{ consumed}}$$

will be even higher than that which is found when glucose is oxidized. Bleibtreu¹ obtained quotients as high as 1.33 in geese stuffed with grain. The reader who is interested in the intermediate steps of this reaction will find them discussed by Ringer and Baumann² but we may pass on to the simplest expression of this conversion as given by Bleibtreu.



The glucose contains 4.7 per cent more heat than the fat which is formed. The reaction is therefore exothermic and for every liter of carbon dioxide produced in this reaction we can reckon on the liberation of 0.8 calories. In a respiration experiment it is easy to find the liters of carbon dioxide which exceed the amount necessary to give a non-protein respiratory quotient of 1. This figure is then multiplied by 0.8, a factor which, of course, is much lower than that of 5.047, the calorific value of 1 liter of carbon dioxide or 1 liter of oxygen when carbohydrate is burned.

There is little evidence at the present time regarding the formation of fat from protein in the human body. Theoretically this may take place since about one-half of the protein molecule is converted into glucose in its normal combustion.

¹ Bleibtreu: *Pflüger's Archiv*, 1901, **85**, 345. Quoted by Lusk, *Science of Nutrition*, 1917, p. 306.

² Ringer and Baumann: *Endocrinology and Metabolism*, New York, Appleton & Co., 1923, **3**, 268.

Atkinson, Rapport and Lusk¹ have demonstrated by calorimeter experiments on a dog that after the ingestion of meat in very large quantities, there is a conversion of protein into fat as the dominant feature of the process.

From a chemical standpoint it is easy to conceive of the conversion of the glycerol radical of fat into carbohydrate in the animal body and this probably takes place in man. The glycerol forms such a small proportion of the fat molecule that the subject is of little importance except in diabetes and we shall therefore discuss it under this heading. In the same place we shall consider the respiratory quotients and caloric values when fat is incompletely oxidized resulting in the excretion of ketone bodies in the urine.

THE METABOLISM OF PROTEINS.

The proteins are the most important constituents of the body since they form the great mass of all actively functioning organs. Fats and carbohydrates, comparatively speaking, are mere deposits of foodstuffs. Proteins constitute about 19 per cent of the human body and the average man who weighs 154 pounds (70 kg.) contains about 13.1 kg. proteins or 2100 grams of nitrogen.

Overnutrition adds comparatively little to the true protein which forms a permanent part of the body. After the ingestion of a large amount of this foodstuff, an extra quantity of protein is held temporarily in the body and upon the cessation of the high-protein diet is gradually eliminated from the cells in which it was stored. This was called "circulating protein" by Voit,² "surplus cellular nitrogen" by Benedict and his associates.³ The more generally accepted term is "deposit protein" as used by Lusk.

The protein molecules are extremely complex being formed by a large number of amino-acids. Rough estimates give them molecular weights of 14,000 to 16,000. Dry muscle protein contains 15 to 17.5 per cent nitrogen and 0.3 to 2 per cent sulphur, the latter being found in the amino-acid cystin. Lean muscle in the body is about 70 per cent water

¹ Atkinson, Rapport and Lusk: *Jour. Biol. Chem.*, 1922, **53**, 155.

² Voit: See Lusk (*Science of Nutrition*, 3d ed., 1917, p. 85).

³ Benedict, Miles, Roth and Smith: *Carnegie Institution of Washington Publication No. 280*, 1919.

and 100 grams of lean beef represent about 3 grams of nitrogen. Ingested into the stomach proteins are quickly attacked by the hydrochloric acid and pepsin and broken down to proteases, peptones and polypeptids. In the intestine the trypsin and erepsin carry these through the dipeptid stage and form the amino-acids which are absorbed into the blood stream. In this they are transported to the cells of the body. Here they serve to replace the "wear and tear" of tissue waste being resynthesized into body protein. The excess of amino-acids usually present is oxidized to furnish energy just as in the case of fat and carbohydrate. The process of digestion, absorption and oxidation is begun rather rapidly as is shown by the following curves for the elimination of nitrogen and sulphur:

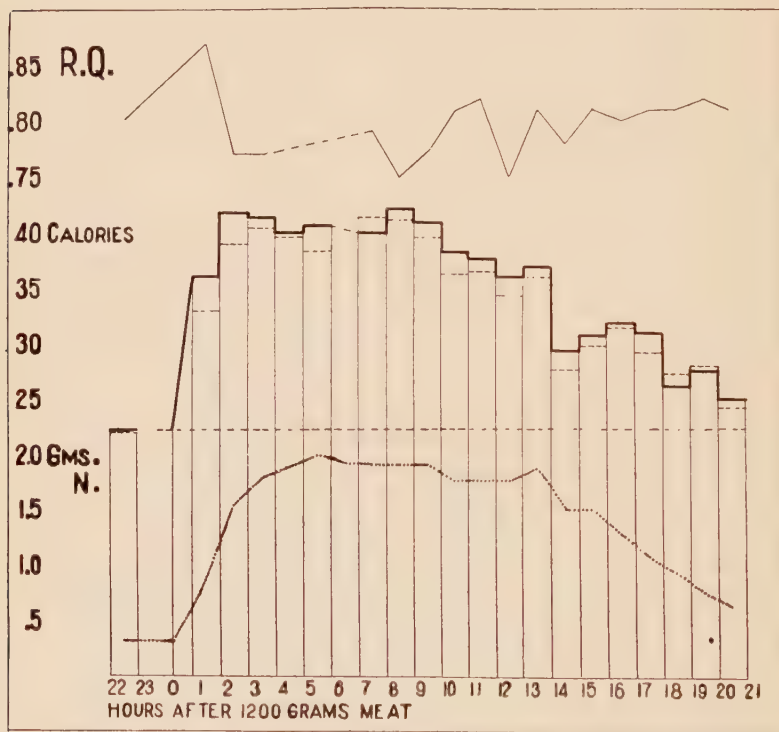


FIG. 2.—Showing the respiratory quotient, the total metabolism determined by indirect (heavy black line) and direct (broken line) calorimetry as well as the nitrogen elimination (dotted line) during hourly periods after the ingestion of 1200 grams of meat by a small dog. (From Lusk.)

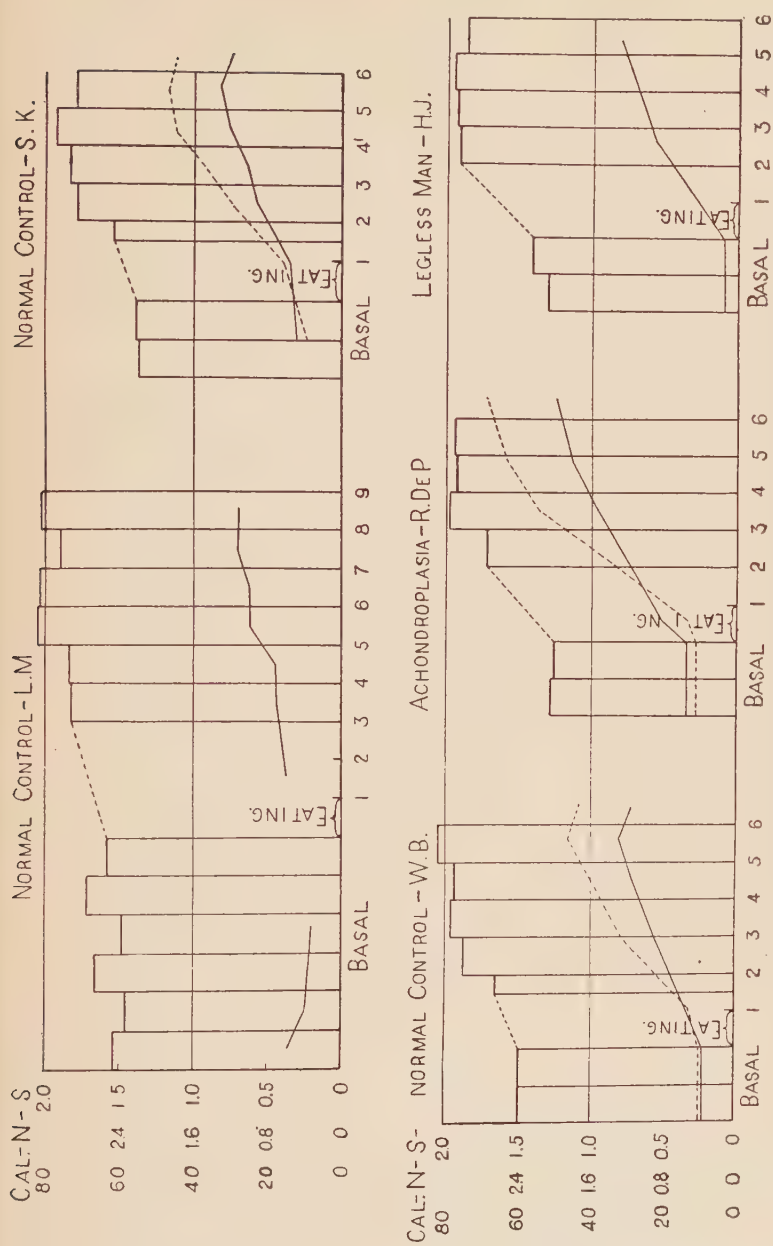


FIG. 3.—Specific dynamic action of protein. Columns show the basal heat production in calories per hour and in the increased metabolism after the man has eaten chopped beef containing 23 to 25 grams of nitrogen. The dotted line represents the excretion of sulphur in the urine in decigrams. The continued line gives the nitrogen elimination in grams. (Aub and DuBois.)

As the amino-acids circulate in the blood they cause a stimulation of the oxidative process in the body cells. This phenomenon which is called the "specific dynamic action" will be discussed in a subsequent chapter. When amino-acids are used in the resynthesis of proteins to replace the wear and tear of the body cells this specific dynamic action is not manifest.

TABLE 2.—SUMMARY OF NITROGEN MINIMUM EXPERIMENTS ON NORMALS. (FROM McCANN.)

Author and subject.	Length of experiment, days.	Day of experiment.	Total calories in food.	Calories per kg., body weight.	Body weight, kg.	Food N., gm.	Urine N., gm.	Fecal N., gm.	Total N., gm.	Nitrogen balance, gm.	Food N. per kg., gm.	Urine N. per kg., gm.	Calories from carbohydrate, per cent.	Reference No.
Hirschfeld II 1888	8	6-8	3462	47.0	73.0	7.46	5.76	1.65	7.41	+0.05	0.102	0.079	..	(A)
Klemperer II 1889	8	6-8	5020	77.0	65.3	5.28	2.51	1.02	3.53	+1.75	0.081	0.038	38	(B)
Sivén 1898	43	42	2441	42.0	58.9	2.43	1.78	1.33	3.17	-0.74	0.041	0.030	67	(C)
Landergren 1903	II	4	3374	45.2	73.4	0.82	3.76	0.75	4.51	-3.69	0.011	0.051	95	(D)
III	4	4	3163	37.8	79.1	2.50	3.95	1.47	5.42	-2.92	0.032	0.050	52	
IV	4	4	2920	45.0	62.4	2.05	3.04	1.02	4.06	-2.01	0.033	0.049	44	
V	4	4	3089	38.4	77.3	2.40	4.20	1.33	5.53	-2.13	0.031	0.054	43	
VI	4	4	2745	36.1	73.4	2.20	4.95	1.28	6.23	-4.03	0.030	0.067	53	
Hindhede 7 (Madsen) VII-15	19	Av. per.	3796	53.0	71.5	3.62	3.41	+0.21	0.051	0.048	61	(E)
Kocher														
R. A. K.	10	5	5089	64.0	79.2	1.01	2.92	1.16	4.08	-3.07	0.013	0.037	100	(F)
J. G. F.	10	4	5089	72.0	70.4	1.01	2.89	1.13	4.02	-3.01	0.014	0.041	100	

(A) Hirschfeld: Virchow's Arch., 1888, 114, 301.

(B) Klemperer: Ztschr. f. klin. Med., 1889, 16, 550.

(C) Sivén: Skand. Arch. f. Physiol., 1900, 10, 91.

(D) Landergren: Skand. Arch. f. Physiol., 1903, 14, 112.

(E) Hindhede: Skand. Arch. f. Physiol., 1913, 30, 97.

(F) Kocher: Deutsch. Arch. f. klin. Med., 1914, 115, 81.

When protein is metabolized the sulphur which it contains is promptly eliminated and after a short interval the nitrogen also, provided the kidneys are not diseased. This nitrogen excretion in the urine is used in experiments as an index of protein metabolism, and if a subject during a certain period excretes 1 gram of nitrogen we estimate that he has oxidized during that period 6.25 grams of protein. For most practical purposes we disregard the slight lag in excretion.

Under ordinary circumstances in health the excretion of nitrogen corresponds fairly closely to the ingestion and the individual remains in what is called "nitrogen balance." Such an equilibrium may be established at a high level if the man is accustomed to consume large amounts of meat and other protein containing foods. With the dietary habits of the present generation most people maintain themselves in balance with an intake of 12 to 19 grams of nitrogen a day (75 to 118 grams of protein). Equilibrium can be established and maintained for long periods at as low a level as 3 to 7 grams per day provided that the diet contain sufficient total calories to cover the daily expenditure. A "nitrogen minimum" can be reached with an excretion of 2.2 to 4 grams a day if certain precautions are taken. The protein of the food must contain less than 3 grams nitrogen and the total caloric intake must amply cover the energy expenditure and a sufficient proportion must be in the form of carbohydrate calories. The protein itself must be of a composition which corresponds fairly closely to human muscle protein in its content of the various amino-acids. The proteins of meat, eggs and milk are suitable. Gelatine or the incomplete proteins of maize cannot replace the wastage of body tissues.

This nitrogen minimum was called the "wear and tear" quota by Rubner¹ and it has been the subject of many studies by him and his pupil Karl Thomas.² Landegren,³ Chittenden⁴ and others, have made numerous investigations on low-protein diets. The subject was discussed by McCann⁵ in 1922 and also by Friedrich Müller,⁶ and more recent studies have been made by Lauter and Jenke⁷ who have reviewed the literature and made the most important contribution to our knowledge of the nitrogen minimum in various diseases. Their normal controls on suitable diets have excreted between 1.8 and 3.4 grams of nitrogen per day. M. Smith⁸ has reached the low figure of 1.58 grams of nitrogen per day in the case of a healthy medical student.

¹ Rubner: *Arch. f. Hyg.*, 1908, **66**, 1.

² Thomas: *Arch. f. Physiol.*, 1909, p. 218; *ibid.*, 1910, p. 249.

³ Landegren: *Skand. Arch. f. Physiol.*, 1903, **14**, 112.

⁴ Chittenden: *Physiological Economy in Nutrition*, 1904.

⁵ McCann: *Arch. Int. Med.*, 1922, **29**, 33.

⁶ Müller: *Deutsch. med. Wehnschr.*, 1922, **48**, 513.

⁷ Lauter and Jenke: *Deutsch. Arch. f. klin. Med.*, 1925, **146**, 323; *Ibid.*, 1925, **146**, 173.

⁸ M. Smith: *Jour. Biol. Chem.*, 1926, **68**, 15.

Although it has been clearly demonstrated that man can live on an intake of 3 to 7 grams of nitrogen a day, experience has shown that for most people life on such a diet is singularly unattractive.

In disease there may be distinct changes in the protein metabolism. Infectious diseases with toxemia, cancer, and other wasting illnesses are accompanied by what is called a "toxic destruction of protein." Under such conditions the nitrogen excretion remains higher than the intake. Patients who are given in their diet, say 10 grams of nitrogen, may excrete 25 grams and if there is a forced intake of 25 grams excretion climbs 5 to 10 grams higher. As Shaffer and Coleman¹ have shown in typhoid fever you can bring the patient into balance if you give 3500 to 4500 calories in the food but this is about double the number of calories actually produced by the patient's metabolism. Moreover, the "nitrogen minimum" is raised in such toxic diseases and Shaffer and Coleman, Kocher² and others could not reduce the nitrogen excretion below 7 to 15 grams a day even on an ample dietary which contained only 2 to 4 grams of nitrogen. This interesting phase of protein metabolism will be discussed more fully later.

Many people, and particularly the laity, have the idea that protein food is consumed in muscular exercise. This erroneous conception should have been completely dispelled many years ago by the classical experiment of Fick and Wislicenus.³ These investigators climbed the Faulhorn and expended three times as much energy as could have been furnished by the protein metabolized during the period of their walk.

Karl Thomas⁴ and R. A. Kocher have demonstrated the same fact even more clearly. Kocher who established his nitrogen output at about 3 grams per day when doing quiet laboratory work walked 60 kilometers in one day and found that the nitrogen excretion only rose to 3.8 grams. On this day he must have derived about 2 per cent of his calories from protein.

Curiously enough the nitrogen of the feces is composed only in small part of unabsorbed food. Most of it is derived from

¹ Shaffer and Coleman: *Arch. Int. Med.*, 1909, **4**, 538.

² Kocher: *Deutsch. Arch. f. klin. Med.*, 1914, **115**, 81.

³ Fick and Wislicenus: *Myothermische Untersuchungen*, 1889.

⁴ Thomas: *Arch. f. Physiol.*, 1910, supplement volume, p. 249.

the secretion of the gastro-intestinal tract, the débris from the intestinal walls and the bodies of the bacteria which inhabit the gut. Of course if an individual eats large amounts of indigestible protein such as over-cooked meat or coarse vegetables there will be a considerable amount of unabsorbed food. Again in certain diseases with intestinal disturbances and diarrhea, the feces nitrogen may rise to abnormal levels. Under ordinary conditions, however, the protein is all absorbed and the stools contain daily about 1 gram of nitrogen derived from the intestinal tract. In metabolism experiments this should be determined by actual analysis though many estimate the feces nitrogen as 1 gram per day or else as 10 per cent of the nitrogen intake. This feces nitrogen is added to the urinary nitrogen in estimating the total protein metabolism.¹ One gram of such total nitrogen represents 6.25 grams of protein metabolized or destroyed.

The mathematics of the protein metabolism is somewhat complicated, since the oxidation is not complete as in the case of carbohydrates and fats.

The best known computation is that of Loewy:² 100 grams of meat protein contain:

52.38 g. C 7.27 g. H 22.68 g. O 16.65 g. N 1.02 g. S

of which is eliminated in the urine:

9.406 g. C 2.663 g. H 14.099 g. O 16.28 g. N 1.02 g. S

in the feces:

1.471 g. C 0.212 g. H 0.889 g. O 0.37 g. N

leaving a residuum for the respiratory processes of:

41.50 g. C 4.40 g. H 7.69 g. O

deduct intramolecular water:

	0.961	7.69
41.50 g. C	3.439 g. H	

We notice that as in the case of fat there is not enough intramolecular oxygen to oxidize the hydrogen. Therefore, it

¹ Lusk: Science of Nutrition, 1917, p. 39.

² Loewy: Oppenheimer's Handb. der Biochemie, 1911, 4, I, 279. Quoted by Lusk, p. 60.

will require 138.18 grams of oxygen to oxidize both carbon and hydrogen. This will produce 152.17 grams CO_2 . Changing the oxygen and hydrogen to liters in order to obtain the respiratory quotient in the usual manner we find

$$\frac{77.39 \text{ L } \text{CO}_2}{96.63 \text{ L } \text{O}_2} = 0.801 \text{ R.Q.}$$

We can see that the metabolism of 100 grams of protein will cause the elimination of 16.28 grams of nitrogen in the urine, the production of 152.17 grams of CO_2 and the absorption of 138.18 grams of oxygen. This gives us the lead for a most useful calculation. We find that 1 gram of urinary nitrogen represents the production of 9.35 grams carbon dioxide and the absorption of 8.45 grams of oxygen which must be ascribed to the metabolism of protein. If therefore we make a respiration experiment and at the same time determine the nitrogen output in the urine we can deduct the proper amounts from the total oxygen absorption and carbon dioxide excretion and ascribe the remainder to the metabolism of fat and carbohydrate. The next step is simple. We divide the volume of this carbon dioxide by the volume of the oxygen and thus obtain the non-protein respiratory quotient. Since the respiratory quotient of carbohydrate is 1.00 and the respiratory quotient of fat is 0.707 we can calculate the relative proportion of fat and carbohydrate from any non-protein respiratory quotient between these two points. For convenience we use the table prepared by Zuntz and Schumburg.¹ This calculation which will be given in detail further on should be made in all exact studies of the respiratory metabolism. For clinical purposes, however, we estimate that a normal man fourteen hours after his last meal is deriving 15 per cent of his calories from protein and make our calculations accordingly. This saves the labor of collecting and analyzing the urine and if we are measuring the basal metabolism does not introduce an error of more than 1 per cent. A few clinicians have neglected the protein metabolism in their calculations entirely, but this is done through gross ignorance since it is just as easy to use tables based on 15 per cent of the metabolism from protein and if this factor is not taken into consideration all of their calculations will be about 1 per cent too high.

¹ Zuntz and Schumburg: Studien zu einer Physiologie des Marsches, Berlin, 1901, p. 361. See also Lusk, Jour. Biol. Chem., 1924, 59, 41.

TABLE 3.—THE NON-PROTEIN RESPIRATORY QUOTIENT. ANALYSIS OF THE OXIDATION OF MIXTURES OF CARBOHYDRATE AND FAT.

(TABLE OF ZUNTZ AND SCHUMBURG MODIFIED BY LUSK.)

R. Q.	Percentage of total oxygen consumed.		Percentage of total heat produced.		Calories per liter O ₂ .	
	Carbo- hydrate.	Fat.	Carbo- hydrate.	Fat.	Number.	Logarithm.
	(1)	(2)	(3)	(4)	(5)	(6)
0.707	0	100.00	0	100.00	4.686	0.67080
0.710	1.00	99.00	1.10	98.90	4.690	0.67114
0.720	4.40	95.60	4.80	95.20	4.702	0.67228
0.730	7.80	92.20	8.40	91.60	4.714	0.67342
0.740	11.30	88.70	12.00	88.00	4.727	0.67456
0.750	14.70	85.30	15.60	84.40	4.739	0.67569
0.760	18.10	81.90	19.20	80.80	4.751	0.67682
0.770	21.50	78.50	22.80	77.20	4.764	0.67794
0.780	24.90	75.10	26.30	73.70	4.776	0.67906
0.790	28.30	71.70	29.90	70.10	4.788	0.68018
0.800	31.70	68.30	33.40	66.60	4.801	0.68129
0.810	35.20	64.80	36.90	63.10	4.813	0.68241
0.820	38.60	61.40	40.30	59.70	4.825	0.68352
0.830	42.00	58.00	43.80	56.20	4.838	0.68463
0.840	45.40	54.60	47.20	52.80	4.850	0.68573
0.850	48.80	51.20	50.70	49.30	4.862	0.68683
0.860	52.20	47.80	54.10	45.90	4.875	0.68793
0.870	55.60	44.40	57.50	42.50	4.887	0.68903
0.880	59.00	41.00	60.80	39.20	4.899	0.69012
0.890	62.50	37.50	64.20	35.80	4.911	0.69121
0.900	65.90	34.10	67.50	32.50	4.924	0.69230
0.910	69.30	30.70	70.80	29.20	4.936	0.69339
0.920	72.70	27.30	74.10	25.90	4.948	0.69447
0.930	76.10	23.90	77.40	22.60	4.961	0.69555
0.940	79.50	20.50	80.70	19.30	4.973	0.69663
0.950	82.90	17.10	84.00	16.00	4.985	0.69770
0.960	86.30	13.70	87.20	12.80	4.998	0.69877
0.970	89.80	10.20	90.40	9.60	5.010	0.69984
0.980	93.20	6.80	93.60	6.40	5.022	0.70091
0.990	96.60	3.40	96.80	3.20	5.035	0.70197
1.000	100.00	0	100.00	0	5.047	0.70303

Formula for
column.

(R. Q. = R.)

 $R - 0.707$

$$(1) \quad \text{Per cent} = 100 \frac{0.293}{1.00 - R}$$

$$(2) \quad \text{Per cent} = 100 \frac{0.293}{504.7 (R - 0.707)}$$

$$(3) \quad \text{Per cent} = \frac{5.047 (R - 0.707) + 4.686 (1.00 - R)}{468.6 (1.00 - R)}$$

$$(4) \quad \text{Per cent} = \frac{5.047 (R - 0.707) + 4.686 (1.00 - R)}{R - 0.707}$$

$$(5) \quad \text{Calories} = 4.686 + \frac{0.293}{R - 0.707} \times 0.361$$

$$(6) \quad \text{Logarithm} = \text{Log. of column 5}$$

When protein is metabolized about 58 per cent of its weight is converted into glucose at one stage of the process. With the normal individual this is usually oxidized immediately and it does not, therefore, enter into our calculations of the total reaction. In phlorhizin diabetes or in severe human diabetes the glucose is excreted in the urine and it is therefore necessary to use the calculations which will be described in the Chapter on Diabetes.

If we reckon the calories available for the body from the food ingested we must use a different calculation.

The caloric value of pure protein burned in a bomb calorimeter is much higher than the figures we use to represent its fuel value to the body. For instance, fat-free beef furnishes 5.3 to 5.7 calories per gram, casein 5.6 to 5.8 calories, egg white 5.7 calories. Rubner worked out the present average standard of 4.1 calories of available energy from 1 gram of protein as follows:

100 gm. of dry muscle furnish		534.5 cal.
Waste in urine as urea, etc.	112.94	
Wastes in feces	16.83	
	<hr/>	129.77
Heat for imbibition of protein (lost on drying)		2.69
Heat for solution of urea		1.99
		<hr/>
Total to be subtracted from bomb value		134.45
Remaining available for body		400.00 cal.

This figure Rubner altered to 4.1 to represent more nearly the average of the proteins of the food.

We must remember that Rubner has allowed for a small part of losses of nitrogen in the feces in calculating this factor of 4.1, but if there is high percentage loss due to intestinal disease or indigestible food, we must subtract for this excess.

Atwater by a slightly different process of calculation adopted the heat value of 4.25 calories per gram of meat protein and 3.87 calories per gram of vegetable protein. This last figure was based on some evidence that only 85 per cent of proteins in cereals was absorbed. More recent work shows that about 92 per cent is absorbed and this would raise the available calories to 3.98 per gram of vegetable protein.

THE MIXTURES OF PROTEIN, FAT AND CARBOHYDRATE METABOLIZED IN THE BODY.

In the previous pages we have considered each foodstuff by itself. For practical purposes we must consider all three at the same time, since the human body is always oxidizing all three. This is rather a sweeping statement, as some believe that in complete diabetes there is no oxidation of carbohydrate and there is a possibility that under certain conditions of fat formation there is no oxidation of fat. I do not think that there is the slightest reason to believe that the body ever gets along without the oxidation of protein.

In an effort to show graphically, to the readers of this book, the relationships of these three substances, the writer¹ has constructed a triangular map of the metabolism somewhat resembling the food map of Irving Fisher.²

In each triangle the lower left-hand corner, at the respiratory quotient of 0.707, represents the theoretical point at which 100 per cent of the calories are derived from fat, the lower right-hand corner, over the respiratory quotient of 1.00, represents the point, never quite attained, where all of the calories would be derived from carbohydrate. The peak, which is never even approached in man, is set at the point where 100 per cent of the calories would be derived from protein. This peak is, of course, placed directly over the respiratory quotient of 0.801. The subdivisions on the base line, as we have said before, are made according to the formulæ given by Lusk.³ The subdivisions on the side lines are made according to similar formulæ, using the appropriate factors for protein. In Fig. 4 these subdivisions are unevenly spaced on account of the nature of the formulæ.

By means of Fig. 4 we can rapidly find the percentage of calories furnished by carbohydrate if we know the total respiratory quotient and the percentage of calories furnished by protein.

The abscissæ represent the total respiratory quotient; the ordinates on the left-hand side of the chart, the percentage of calories from protein. The percentage from carbohydrate is determined from the diagonal lines with the figures on the

¹ Du Bois: *Clin. Cal.* 35, *Jour. Biol. Chem.*, 1924, 59, 43.

² Fisher: *Am. Jour. Physiol.*, 1906, 15, 417; *Jour. Am. Med. Assn.*, 1907, 48, 1316.

³ Lusk: *Jour. Biol. Chem.*, 1924, 59, 41.

right side of the triangle. Adding the percentages from protein and carbohydrate, we subtract this sum from 100 and find the percentage from fat. For example, if the respiratory quotient were 0.9 and protein furnished 20 per cent of the calories, we see that carbohydrate furnished 61 per cent and fat 19 per cent.

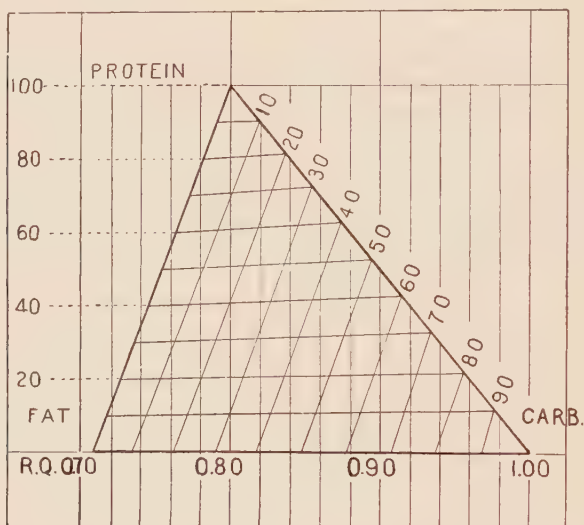


FIG. 4.—Diagram showing the percentages of calories derived from protein, fat and carbohydrate according to the respiratory quotient. The base-line gives the total respiratory quotient; the ordinates reading on the left-hand side give the percentage of calories from protein; the diagonals reading on the right of the triangle give the percentage from carbohydrate.

Using this triangle as a map we can show the various zones into which the human organism travels under the influence of the different foodstuffs. It is obvious that after a meal containing a large amount of meat the organism will derive a greater percentage of its calories from this source. After the ingestion of sugar in large amounts the body will derive almost all its energy from carbohydrate and during starvation or the administration of a diet low in carbohydrate, fat will furnish most of the energy, a certain share, of course, being contributed by protein. Under ordinary conditions most of us find ourselves in the lower part of the triangle, in that zone where 10 to 20 per cent of the calories come from protein and 20 to 70 per cent from carbohydrate. The Hindoos and Chi-

nese, on a diet which consists largely of rice, live in the lower right-hand corner of the triangle, the Eskimos, who eat seal, fish and blubber exist near the left-hand border of the triangle since they derive only minimal percentages of their energy from carbohydrate.

In order to demonstrate the changes in metabolism a map is introduced at this point, showing the results in certain calorimeter experiments which are discussed in much greater detail in other chapters.

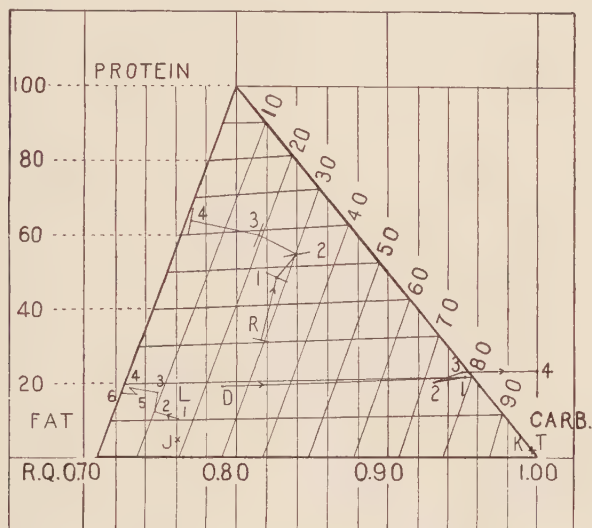


FIG. 5.—Triangles used to show changes in metabolism. *R*, the effect of a large protein meal; *D*, the effect of 200 gram of glucose; *L*, the first six days of starvation; *KT* and *J*, low-protein diets with muscular exercise.

In Fig. 5 we have drawn lines which show the course of the metabolism during certain experiments in the calorimeter. The point *R* gives the position of the basal metabolism of the achondroplastic dwarf, Raphael de P.¹ on March 15, 1916. On this line the Fig. 4 represents his metabolism the next day in the period starting one hour after he had finished eating a breakfast consisting of chopped beef, containing 23.2 grams of nitrogen. This was an enormous meal for a dwarf weighing 90 pounds. It will be noted that during the second, third and

¹ Aub, J. C., and Du Bois, E. F.: Clin. Cal. 21, Arch. Int. Med., 1917, 19, 842.

fourth hours the percentage of calories derived from protein rose until it reached 64 per cent, perhaps the highest percentage ever demonstrated in a respiration experiment on a man. During the fourth hour, metabolism was on an exclusively protein-fat basis, similar to that of the Eskimos, but, as we shall see later, safely beyond the zone of ketosis. In this graph we have shown the specific dynamic action and the increase in metabolism due to the protein meal by drawing cross lines whose length is proportional to the height of the metabolism. Lower in this figure the letter *D* represents the

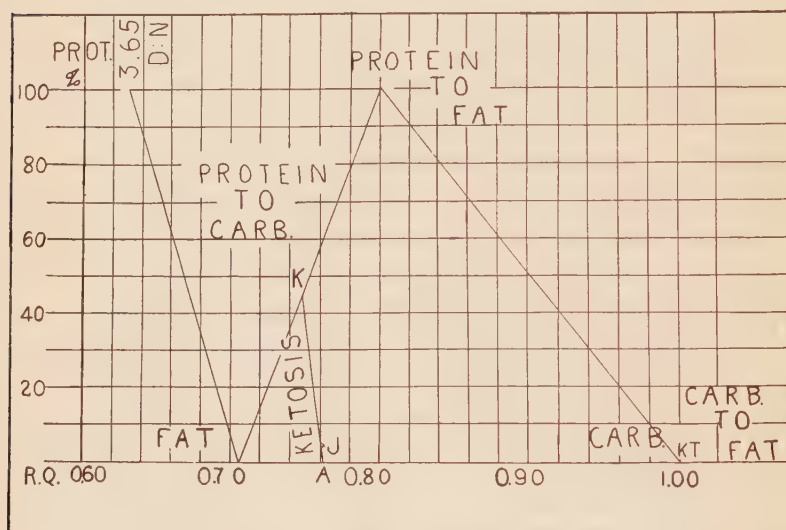


FIG. 6.—Zones of metabolism.

position of the usual basal metabolism of the normal control, E. F. D. B.¹ The point *I* on this line shows the position in the calorimeter period starting one hour after he had taken 200 grams of dextrose on May 8, 1914. In the next period there was a slight fall in quotient but a subsequent rise to 1. In the lower left-hand corner, the line *L* represents the metabolism of Benedict's² subject, Levanzin during the first six days of his fast.

¹ Gephart, F. C., and Du Bois, E. F.: *Clinical Cal.* 4, *Arch. Int. Med.*, 1915, 15, 835.

² Benedict, F. G.: *Carnegie Institution of Washington Publication No. 203*, 1915.

There are certain positions outside the triangle which are of importance from a metabolic standpoint, as shown in Fig. 6. To the right of the carbohydrate corner there is a zone in which the organism is transforming carbohydrate into fat and it is of interest to note that this may occur with quotients below 1.00 when any considerable portion of protein is being metabolized. With very excessive amounts of protein, such as have been attained in dog experiments by Lusk,¹ protein can be partially transformed to fat and deposited as such.

To the left of the original triangle, is a second triangle which represents the conversion of a portion of the protein molecule into carbohydrate and its storage as glycogen or excretion as glucose. Lusk² has shown that the respiratory quotient falls as low as 0.632 if, during the metabolism of 100 grams of beef protein, 59.41 grams of glucose, derived from this protein, is excreted in the urine (dextrose-nitrogen ratio = 3.65). It is only in the lower portion of this triangle that we find patients with diabetes, since they seldom derive more than 35 per cent of their calories from protein.

The line *KA* in the "fat corner" shows a region in which there is ketosis since the proportion of carbohydrate is so low that the fats are incompletely oxidized. This will be discussed more fully when we come to diabetes.

There is a narrow zone along the bottom of this chart which is probably never reached by man, since we can conceive with difficulty of a state in which protein furnishes less than 1 per cent of the total calories. Perhaps the lowest percentage yet demonstrated is the 1.5 per cent attained by Karl Thomas³ in a nitrogen minimum experiment in which, on an extremely low-protein diet, he performed a large amount of work on an ergometer. This is shown by the point *KT* in Figs. 5 and 6. The lowest point near the "fat" end of the scale that I have been able to find was the old experiment of Atwater and Benedict⁴ on the subject, J. C. W., who expended 9981 calories in a single work day while he was on a diet containing 5138 calories.

We must remember that this chart shows only the net transformations within the body and expresses the actual

¹ Lusk, G.: *Jour. Biol. Chem.*, 1922, **53**, 155.

² Lusk, G.: *Arch. Int. Med.*, 1915, **15**, 939.

³ Thomas, K.: *Arch. f. Physiol., Suppl.*, 1910, p. 249.

⁴ Atwater, W. O., and Benedict, F. G.: United States Department of Agriculture Bulletin No. 136, 1903, Tables 100 and 126.

loss of protein, fat and carbohydrate in a given period. It is quite possible that fat is deposited in one part of the body while it is being withdrawn from another organ for purposes of combustion. Krogh and Lindhart¹ have recently emphasized the probability of extensive transformations of this nature.

A neglected but important fact has been emphasized by Richardson² in a paper entitled: "The Inadequacy of the Measured Diet as an Index of the Food Metabolized." The food which the patient metabolizes is seldom the same as that which the doctor orders. Protein, fat and carbohydrate may be withdrawn from or stored in the body.

The subject of metabolism during muscular exercise seems out of place in a book on basal metabolism, but it is impossible to pass it by without brief mention. In the last few years A. V. Hill and his coworkers^{3,4} have brought forward evidence which seems to indicate that during short periods of vigorous exercise the work is accomplished through the combustion of carbohydrate alone. Furusawa⁵ working under Hill, has found that in long continued exercise fat also contributes to the metabolism. Hill's theory that carbohydrate alone furnished the muscular energy and that fat was converted into carbohydrate before oxidation has been vigorously combated by Lusk^{6,7} and his pupils.

THE INFLUENCE OF FOOD ON THE RESPIRATORY METABOLISM.

This subject does not belong to a discussion of the basal metabolism which is always measured after the stimulating influence of food has ceased. It is of importance for the clinician to be able to estimate the effect of food in increasing the total metabolism if he wishes to determine the main-

¹ Krogh, A., and Lindhart: *Biochem. Jour.*, 1920, **14**, 290.

² Richardson, H. B.: *Boston Med. and Surg. Jour.*, 1923, **189**, 813.

³ Hill, A. V.: *Lectures on Nutrition*, 1924-1925, Mayo Foundation, W. B. Saunders Company, Philadelphia and London, 1925, p. 109.

⁴ Hill, A. V., Long and Lupton: *Proc. Roy. Soc. B.*, 1924, **96**, 438, 444, 455; **97**, 84, 127, 155, 167.

⁵ Furusawa: *Ibid*, 1926, **99**, 155.

⁶ Lusk: *Biochem. Ztschr.*, 1925, **156**, 334.

⁷ Du Bois, E. F.: *Lectures on Nutrition*, 1924-1925, Mayo Foundation, W. B. Saunders Company, Philadelphia and London, 1925, p. 77.

tenance ratios since he must add a certain amount for this factor, as well as for bodily activity. An attempt will be made to give the data needed for such estimations, but it is impossible to review the whole subject or devote much time to the theoretical aspects of this difficult but fascinating field of science.

The best discussion has been given by Lusk^{1,2} who has made accessible the work and theories of Rubner and has himself modified these in many ways. Benedict and Carpenter³ devote 36 pages to a review of previous work done with human subjects, and add many experiments of their own.

Carpenter⁴ has recently published an extensive investigation of the respiratory exchanges following enemata containing alcohol and dextrose. Clinicians have for many years been seeking to find some aid in diagnosis and treatment through changes in the specific dynamic action in disease. Among those who have recently published studies of this nature are Plaut, Knipping, Strouse, Göttche,⁵ Pollitzer and Stolz⁶ and Lauter.⁷ For a discussion of their results, which are not very impressive, the reader is referred to the critique by Lauter and the comments in the chapter on Obesity.

The effect of the various classes of food in stimulating the metabolism is best shown by Lusk's calorimeter experiments on dogs.⁸ His well-trained experimental animals would take enormous amounts of the foods and lie perfectly quiet during long periods in the respiration chamber. One of the charts is reproduced on page 32. The small dog ate a large amount of meat, more than most men could swallow and during the period of two to ten hours later gave off almost twice as much heat as before the meal. The increase in heat production followed closely the curve of nitrogen elimination which

¹ Lusk: *Science of Nutrition*, third edition, Philadelphia and London, W. B. Saunders Company, 1917.

² Lusk: *Medicine*, 1922, **1**, 311.

³ Benedict and Carpenter: *Carnegie Institution of Washington Publication No. 261*, 1918.

⁴ Carpenter, T. M.: *Human Metabolism with Enemata of Alcohol, Dextrose, and Levulose*, Carnegie Institute of Washington, 1925, Publication No. 369.

⁵ Göttche, O.: *Klin. Wchnschr.*, 1925, **4**, 2062.

⁶ Pollitzer and Stolz: *Wien. Arch. f. inn. Med.*, 1924, **9**, 307; 1925, **10**, 137; 1925, **11**, 319.

⁷ Lauter, S.: *Deutsch. Arch. f. Klin. Med.*, 1926, **150**, 315.

⁸ Lusk: *Science of Nutrition*, third edition, Fig. 15, p. 224.

indicates the rate of protein metabolism. No rise is caused by the ingestion of bones, or water or meat extract or urea or sodium chloride. The metabolism is, however, increased by the ingestion of the amino-acids, for instance glycocoll or alanine. On the other hand leucin and tryosin have slight effect and glutamic acid none. In one experiment Lusk found that the entire energy content of the ingested glycocoll reappeared in the extra output of energy given off by the dog in the form of heat. He then gave glycocoll to a phlorhizinized animal. The metabolism was largely increased in spite of the fact that there was no oxidation of the amino-acid and its entire energy content was eliminated in the urine in the form of sugar and urea. This shows that the cause of the specific dynamic action of glycocoll and alanin lies in a chemical stimulation of the cells causing them to metabolize more material. The metabolism products of amino-acids such as glycollic or lactic acids are probably the actual agents of the stimulation. There seems to be no such specific dynamic action when protein is deposited in the form of new tissues.

The specific dynamic action of fat is less marked. Magnus-Levy¹ gave a dog 140 grams of fat bacon and found a rise of about 10 per cent from the third to the eighth hours. After 320 grams of bacon there was a maximal rise of 19 per cent from the third to the sixth hour and the metabolism did not return to its basal level for thirteen hours. About 2.5 per cent of the fuel value of the fat was given off as waste heat.

A rapid rise in metabolism occurs after the ingestion of carbohydrate and at the same time there is a similar rise in the respiratory quotient. Lusk has found the following relationship in the stimulus produced by 50 grams of different sugars given to a dog.

TABLE 4.—INFLUENCE OF 50 GRAMS OF VARIOUS CARBOHYDRATES UPON THE METABOLISM OF A DOG. (LUSK.)

Sugar, 50 grams.	Average R. Q.	Percentage of increase over basal metabolism 2, 3 and 4 hours.
Glucose	1.00	30
Fructose (levulose)	1.02	37
Sucrose	1.02	34
Galactose	0.93	22
Lactose	0.90	3

¹ Magnus-Levy: Arch. f. d. ges. Physiol., 1894, 55, I.

The galactose was oxidized by the dog with difficulty and the lactose was not oxidized at all. He showed that there is no increase when 10 grams of fructose is given to a phlorhizinized dog and excreted as 10 grams of glucose in the urine. Lusk believes that the increased heat production after the ingestion of carbohydrates lay in a plethora of acetaldehyd molecules, which the cells, within the limits of the definite upper level imposed by self regulation were capable of utilizing. About this level the acetaldehyd molecules are convertible into fat with little loss in the original energy content of the sugar from which they arise.

Lusk has found that if he gives a dog glycocoll and glucose there is a summation of the stimulating effects of the two substances. With Murlin he gave glucose at the time of the highest stimulus from fat ingestion and found a second stimulus superimposed upon that of the fat. When glucose and glycocoll were given so that they entered the circulation at the time of the greatest fat metabolism, the total increase was very nearly equal to the sum of the increases which each of the three materials would have induced alone.

These are the main facts regarding the so-called "specific dynamic action" of foods. The effects in man are similar but less marked because of the limitation of man's stomach. Magnus-Levy¹ obtained beautiful curves in experiments on man, and similar experiments have been made by Gigon² and by the Sage investigators,^{3,4} and by Benedict and Carpenter.⁵

The results can be expressed in many different ways but for the purpose of simplification we shall consider only one. Knowing the basal metabolism of an experimental subject and the level of the metabolism for several hours after giving the food, we can readily find by subtraction the extra calories caused by the stimulus of the food. In almost all the calorimeter experiments we must add some calories for the period which has elapsed between the time the meal was started and the beginning of the experimental period in the chamber. In many of them which were finished while the metabolism was still above its basal level it is necessary to add more

¹ Magnus-Levy: *Arch. f. d. ges. Physiol.*, 1894, **55**, 1.

² Gigon: *Arch. f. d. ges. Physiol.*, 1911, **140**, 509.

³ Gephart and Du Bois: *Clin. Cal.* 4, *Arch. Int. Med.*, 1915, **15**, 835.

⁴ Aub and Du Bois: *Clin. Cal.* 21, *Arch. Int. Med.*, 1917, **19**, 842.

⁵ Benedict and Carpenter: *Carnegie Institution of Washington Publication* No. 261, 1918.

calories for the remaining hours of stimulation. In Table 5 I have made these estimations from the curves of the experimental periods as best I could. This could not be done in Tables 6 and 7 without a great deal of labor, but the length of the experimental periods are given in one of the columns.

If we divide the estimated extra calories by the fuel value of the food in terms of calories we obtain a quotient which Benedict and Carpenter call the "cost of digestion." We shall use this term for want of a better, but we must remember that we might get the same effect from the intravenous administration of glucose. The tables show that the different sugars and moderate-sized mixed meals increase the metabolism by 5 to 6 per cent of their fuel value. A very small breakfast causes a smaller increase, a very heavy breakfast gives figures up to 7.4 per cent. The effect of a large protein ration is striking, giving percentages from 10 to 33. The

TABLE 5.—SUMMARY OF CALORIMETER EXPERIMENTS ON EFFECT OF MIXED DIET IN INCREASING HEAT PRODUCTION.

Subject.	Meals.	Fuel value, cal.	Total N., gm.	Calories, per cent.			Estimated increase in heat, cal.*	Cost of digestion, heat increase divided by fuel value
				Protein.	Fat.	Carbohydrate.		
SAGE CALORIMETER								
	Body wt.							
E. F. D. B.	Small breakfast, 73.9 kg.	222	0.8	9	39	52	5.4	2.4
D. P. B.	Small breakfast, 65.2 kg.	222	0.8	9	39	52	5.4	2.4
L. O'R.	Small breakfast, 45.8 kg.	222	0.8	9	39	52	13.2	5.9
Louis M.	Meat and butter	1564	23.9	41	59	0	99.4	6.3
CHAIR CALORIMETER								
H. L. H.	Moderate supper	1731	7.3	11	21	68	84.0*	4.9
A. L. L.	Heavy breakfast	2720	10.9	10	52	38	198.0*	7.3
A. L. L.	Heavy breakfast	2142	8.0	9	47	44	111.0*	5.2
A. H. M.	Heavy breakfast	4378	19.5	12	56	32	225.0*	5.0
A. H. M.	Heavy breakfast	3936	20.1	13	54	33	290.0*	7.4
H. R. D.	Heavy breakfast	3311	14.6	12	43	45	226.0*	6.8
H. R. D.	Heavy breakfast	3697	17.1	12	54	34	193.0*	5.2
UNIT RESPIRATION APPARATUS								
J. J. C.	Moderate breakfast	796	3.4	11	26	63	45.0	6.0
A. F.	Small breakfast	468	3.0	17	52	31	19.0	4.0

* Increase actually found plus increase estimated for periods between ingestion of food and start of experiment and for period of one to three hours after some of the experiments.

TABLE 6.—SUMMARY OF EXPERIMENTS OF BENEDICT AND CARPENTER.
EFFECTS OF FOOD AND DRINK.

	Duration of period, hours.	Increment of heat.		Cost of digestion, per cent.
		Calories.	Value av., per cent.	
Chewing gum	1 to 2½	7 to 42	17	
Chewing rubber stopper	1½	11 to 16	16	
Water, 200 to 325 cc at 50° to 57° C. .	1 to 2½	-6 to +3	-1	
Water, 500 cc at 11° C.	1	1		
Coffee, 312 to 325 cc at 52° to 60° C. .	1½ to 5½	2 to 46	8	
Beef tea, 269 to 400 cc at 50° to 61.4° C.	5 to 6½	16 to 41	8	
Dextrose, 100 gm. 374 to 385 cal. . .	1½ to 6	6 to 35	18	5
Levulose, 100 gm. 373 to 384 cal. . .	1½ to 5½	12 to 36	24	6
Sucrose, 100 gm. 396 to 422 cal. . .	1 to 4	15 to 36	25	6
Lactose, 100 gm. 374 to 385 cal. . .	1½ to 4½	10 to 22	18	5
Dextrose, 75 gm. 286 to 292 cal. . .	1½ to 3	8 to 19	14	5
Levulose, 75 gm. 280 to 291 cal. . .	1½ to 6¾	10 to 38?	24?	8 ?
Sucrose, 75 gm. 295 to 309 cal. . .	1½ to 5½	9 to 27	15	5
Beefsteak, 362 gm. 790 cal. 17.7 gm. N.	5½	81	23	10
Beefsteak, 249 gm. 418 cal. 11.4 gm. N.	11½	138	18	33
Beefsteak, 182 gm. 305 cal. 8.4 gm. N.	5½	86	25	28
Beefsteak, 177 gm. 298 cal. 8.1 gm. N.	6½	56	15	19
Beefsteak, 150 gm. 245 cal. 7.1 gm. N.	4½	38	13	16
Beefsteak, 150 gm. 234 cal. 6.9 gm. N.	3½	13	6	6
Milk, 500 cc 358 cal. 2.6 gm. N.	4	11	..	3

TABLE 7.—EXPERIMENTS IN SAGE CALORIMETER ON INCREASED HEAT
PRODUCTION AFTER GLUCOSE AND PROTEIN.

	Food.	Fuel value, cal.	Estimated increase in heat, cal.	Heat increase divided by fuel value.
E. F. D. B.	100 gm. glucose	370	25.0	6.7
E. F. D. B.	200 gm. glucose	740	36.0	4.9
L. C. M.	200 gm. glucose	740	44.8	6.1
E. F. D. B.	Casein and egg albumen, 10.5 gm. N.	278	49.9	17.8

figure 33 is probably much nearer the truth because it is evident from the charts of Aub and Du Bois that with excessive amounts of protein the metabolism is only just beginning to fall after six hours. A meal with a moderate protein content does not cause the protein metabolism to rise much above its basal level, but if a small man eats 660 grams of chopped beef, his protein metabolism becomes three times as great as it was before the meal and his heat production rises enormously.

The practical application of this is important. Knowing a man's basal metabolism we may wish to calculate his total metabolism. We must add a certain amount for muscular

activity and an additional amount for the specific dynamic action of the food or "cost of digestion." It would seem safe to add for specific dynamic action an amount which equals 5 to 6 per cent of the calories of the food in most cases where the person is on a maintenance ration. If the diet is below the caloric needs a figure between 2 and 5 per cent might be more accurate. If the diet is very liberal and more than 12 per cent of the calories are in protein the figure should be 6 to 8 per cent. Very high-protein diets would cause two or three times this increase.

Since the standard figures of Rubner of 4.1 calories from each gram of protein or carbohydrate and 9.3 calories for each gram of fat do not fully take into account the losses in the feces we must add an additional 2 per cent. This is the average percentage for normals but the figure is modified by disease and by the nature of the food.

Soderstrom, Barr and Du Bois¹ tried to find a small breakfast that could be allowed in the morning before basal metabolism tests. Five normal subjects were studied after a meal consisting of 30 grams of bread, 8 grams of butter with a cup (200 cc) of caffeine-free coffee containing 10 grams of cane sugar and 60 cc of milk. This caused a slight rise in metabolism in the first three hours and after that there was no apparent stimulation. Dr. and Mrs. F. G. Benedict² improved upon this and gave 1 cup (200 cc) of caffeine-free coffee, 16 milligrams of saccharin, 30 grams of medium cream and 25 grams of potato chips. In 2 normal individuals the oxygen consumption returned to the basal level in less than one hour. Bauer and Blunt³ used a more liberal breakfast of cereal, milk, bread and butter and occasionally fruit when they studied children. Four hours after this meal the metabolism was only 1 per cent higher than the previous basal.

¹ Soderstrom, Barr and Du Bois: *Clin. Cal. 26, Arch. Int. Med.*, 1918, **21**, 613.

² Benedict, C. G., and Benedict, F. G.: *Boston Med. and Surg. Jour.*, 1923, **188**, 849.

³ Bauer and Blunt: *Jour. Biol. Chem.*, 1924, **59**, 77.

CHAPTER III.

A BRIEF REVIEW OF CERTAIN LAWS OF PHYSICS.¹

IN all measurements of the gaseous exchanges, we are constantly referring to certain fundamental laws of physics. Most of us have studied these in school or college but have not had much occasion to review them since that time.

Boyle's Law.—In all calculations of the volume of a gas, we express the results at the standard pressure of 760 millimeters of mercury. Since the barometer seldom stands at exactly this level we must correct for the reading according to the formula $\frac{P}{760}$ in which P equals barometric pressure. This is in accordance with Boyle's Law which may be expressed as follows:

When the volume of a mass of gas is changed, keeping the temperature constant, the pressure varies inversely as the volume; or the product of the pressure by the volume remains constant.

The density of a gas is directly proportional to its pressure at a constant temperature.

Boyle's law is not absolutely exact for high pressures but is within 1 per cent for pressures up to 10 atmospheres. Some gases are slightly more compressible than others.

The law of Charles or Gay-Lussac.—It is also necessary for us in all metabolism experiments to correct for the temperature, since we always express the volume of a gas at the standard temperature of 0° C. The formula for this is $\frac{1}{1 + 0.00367\tau}$, τ being the observed temperature in degrees C. and 0.00367 the reciprocal of 273 which is the absolute zero. This calculation depends on the law of Charles or Gay-Lussac.

“Different gases have nearly equal coefficients of expansion.”

¹ The writer is indebted to the well-known text-books of A. L. Kimball and W. Watson.

The increase of a gas per degree rise in temperature is about $\frac{1}{273}$ of its volume at 0°C .

The volume of a gas is very nearly proportional to its absolute temperature when the pressure is kept constant. So when the volume is kept constant the pressure of the gas is proportional to the absolute temperature.

Avogadro's Law.—Avogadro's law is as follows: The number of molecules per cubic centimeter is the same in all gases at the same temperature and pressure. This is the law that we use in calculating the respiratory quotient. The reader will remember that during the oxidation of carbohydrates the volume of oxygen consumed exactly equals the volume of carbon dioxide produced.

Dalton's Laws.—Dalton's laws are as follows:

1. The pressure exerted by and the quantity of a vapor which saturates a given space are the same for the same temperature whether the space is filled by a gas or a vacuum.

2. The pressure exerted by a mixture of gas and a vapor, of two vapors or of two gases, is equal to the sum of the pressures which each would exert if it occupied the same space alone.

These have a direct bearing on all metabolism experiments since we are usually dealing with mixtures of gases. Water vapor is always present in both the inspired and the expired air.

Solution of Gases in Liquids.—The quantity of gas taken up by a given volume of solvent is proportional to the pressure of the gas, but this of course applies only when there is no chemical reaction between the gas and the solution.

Each gas has a different coefficient of absorption for different liquids.

The absorption of these gases by liquids is an occasional source of error in metabolism experiments. We must remember that some of the gases are absorbed into the body fluids by these physical laws and some are held in chemical combinations which introduce entirely different factors.

Gases vary in density. A cubic foot of dry air weighs about $\frac{1}{13}$ of a pound.

Heat.—Temperature may be defined as that property of the body which determines the flow of heat. The specific heat of a substance is the number of calories required to raise the temperature of a gram of the substance 1°C .

Heat is formed by the combustion of certain substances. Table 8 shows the large calories formed by the combustion of various fuels.

TABLE 8.—HEATS OF COMBUSTION IN CALORIES PER GRAM.

Hydrogen gas	34.5
Anthracite	7.8
Alcohol (absolute)	7.2
Wood	4.0
Charcoal	8.0
Gasoline	12.0

Heat Equivalent of Work.—Joule found that the energy required to heat 1 kilogram of water 1°C . is equal to the work done in raising a weight of 1 kilogram to a height of 427 m. or in other units 778 foot pounds' of work are required to raise the temperature of 1 pound of water 1°F .

The Dissipation of Heat.—When heat energy gradually diffuses through a mass of matter, passing from particle to particle from the warmer toward the colder parts of a body, the process is called conduction.

When heat is carried along by the motion of a stream of gas or liquid, the process is called convection.

A hot body surrounded by a perfect vacuum may give out energy and warm neighboring objects. In this case the energy is transmitted by waves in the ether and the process is called radiation.

Radiation itself cannot be regarded as heat, for unless it is absorbed it does not affect the temperature of the bodies through which it passes.

Radiation.—Newton believed that the rate of cooling is proportional to $t-t'$, or the heat lost per second equals $K(t-t')$ when K is a constant to be determined by experiment. This law is nearly true if the difference between the two temperatures is not large and it is often convenient to use.

Stefan found that the total radiation emitted by a body is proportional to the fourth power of the absolute temperature. Hence the total loss of heat by the body in a unit of time is proportional to the surface area of the body and the fourth power of the absolute temperature of the object minus the fourth power of the absolute temperature of the air. The nature of the surface also enters into the calculation.

The human body loses most of its heat by radiation and conduction. Comparatively little heat is conducted away

from the body surface when we are surrounded by wool, but a large amount is carried away when we are in contact with any large surface of cold water.

Vaporization.—About one-quarter of the calories are lost from the body through the moisture of the skin and lungs when the subject is at rest.

The heat required to change 1 gram of liquid into vapor at the same temperature is known as its latent heat of vaporization.

To evaporate 1 gram of water at 100°C . takes 0.5366 calories. To evaporate 1 gram of water at 0°C . takes 0.5967 calories, at 20°C . 0.586 calories.

Conservation of Energy.—This great principle may be expressed as follows: In any system of bodies which neither receives energy from without nor gives up any, the total amount of energy is unchanged. For a more lengthy discussion, the reader is referred to the text-books of physics. This law applies in metabolism to the oxidations of food which are just as complete within the body as without and also to the transformation of heat into kinetic or potential energy.

CHAPTER IV.

THE GASES OF THE BODY.

INTERNAL AND EXTERNAL RESPIRATION.

TABLE 9.—PROPERTIES OF GASES.

Gas.	Molecular weight.	Coefficient of sol in H ₂ O at 0° C.	Wt. of 1 L., gm.	Vol. of 1 gm. cc.
Oxygen	32.000	0.049	1.4292	0.6997
Carbon dioxide	44.005	1.7	1.9652	0.5089
Nitrogen	28.016	0.023	1.2542	0.7973
Water vapor	18.016			

At this point it is necessary to review briefly some of the properties of gases. The rate of diffusion of the gas is inversely proportional to the square of the atomic weight and the heavy gases spread into mixtures or through membranes much more slowly than do light gases such as hydrogen. In most of the gases two or more atoms are combined to form a molecule which under ordinary circumstances is never divided and we always use the symbol O₂ for oxygen and N₂ for nitrogen. The weight of a molecule of a compound gas such as CO₂ is readily found by adding the weight of 1 atom of carbon to 2 atoms of oxygen. The coefficient of solubility of a gas in a certain liquid does not depend on this molecular weight but on the peculiar property of the gas itself. Every gas is ponderable since it is heavier than a vacuum. As a matter of fact, practically every gas can be reduced to liquid form. We know exactly the volume that will be filled by a gram of gas at 0° C. and a pressure of 760 millimeters of mercury.

According to Boyle's law, the volume of a gas is inversely proportional to the pressure and a gram of gas occupies one-half its previous volume when the pressure rises from 1 atmosphere to 2 atmospheres. The calculation is readily made according to the formula $\frac{P}{760}$, P being pressure. Gases contract with a falling temperature and theoretically shrink

to nothing at the absolute zero ($-273^{\circ}\text{C}.$). Since the expansion is proportional to the temperature we can make our calculations according to the formula: $\frac{I}{I+0.00367 t}$

In mixtures of gases such as we find in air each gas has its partial pressure as represented in millimeters of mercury. For instance, in a mixture at a pressure of 760 mm. Hg. containing 20 per cent oxygen this gas would have a partial pressure or vapor tension of 152 mm. Hg. In a pressure of 2 atmospheres the vapor tension would be doubled. An equal result would be found if the pressure remained at 1 atmosphere and the percentage of the gas were doubled.

For purposes of calculating weights, etc., the gases are assumed to be free from water vapor. In all respiration experiments the air contains varying amounts of this gas depending on the temperature and the extent to which it was exposed to water or moist surfaces. We know that a gas at a certain temperature exposed freely to water will be saturated for this temperature and it is possible to calculate the partial pressure of the water vapor.

In regard to water vapor and nitrogen we need consider only the physics of gases but when we deal with oxygen and carbon dioxide we must consider their chemistry also, since they play an active rather than a passive part in metabolism. Their absorption into and release from the blood are chemical as well as physical.

We have seen in the previous chapters that all the food-stuffs, when they are consumed in the tissues, unite with oxygen and in the process form carbon dioxide. It is now necessary to direct our attention to the manner in which these gases are transported the long distance from the nose to the extremities of the body. Physiologists have divided the process into two parts. The first of these, called the external respiration, keeps the alveoli of the lungs supplied with air of a comparatively uniform composition. The second, called the internal respiration, transports the gases between the alveoli and the tissue cells where the metabolism actually takes place.

It may be helpful to review briefly the physiology of respiration from the view point of the man who is making experiments on the gaseous exchange.

TABLE 10.—COMPOSITION OF RESPIRED AIR.

	O ₂ .	CO ₂ .	N ₂ .
Pure country air (free from moisture)	20.93	0.03	79.04
Expired air (one experiment)	16.02	4.38	79.60
Alveolar air (one experiment)	13.80	5.80	81.40

If we examine the respiratory tract at the end of an ordinary inspiration, we come first to the so-called "dead space." This term applies to the air passages between the nose and the small bronchioles down to the place where the functioning epithelium makes its appearance in the ductulus alveolaris. In normal adults of ordinary size this space contains about 140 cc. From the standpoint of gaseous exchange this air is "dead" and it is expired in almost exactly the same condition as it was inspired. It is of course saturated with moisture at body temperature and there is inevitably a slight admixture with the air of the previous expiration, since air in a tube does not advance as a solid column but rather with eddies and slight differences in rate between the center of the column and the periphery. From the functional standpoint the dead space becomes of importance when the rate of respiration changes. With a respiration rate of 10 per minute the dead space wastes 1400 cc which would be 35 per cent of a minute volume of 4000 cc. If the respiration rate were increased to 20 and the minute volume unchanged, 70 per cent would be wasted.

In all types of respiration apparatus which employ mouth pieces, nose pieces or masks, there is an artificial dead space added to the natural. If this be extensive, it constitutes a rather serious factor which must be taken into consideration, since it necessitates a considerable increase in the labor of breathing.

The "tidal air" which passes in and out of the nose in quiet respiration is composed of the "dead space" air and also the portion which constitutes the effective ventilation. This latter penetrates beyond the small bronchioles and inflates the lungs causing the whole of the expansion. This part of the tidal air in itself fills only a small portion of the functioning alveoli but the oxygen diffuses rapidly into the neighboring alveoli and the carbon dioxide diffuses in the opposite direction. At the time of expiration there is still a considerable difference between the composition of this air and the so-called alveolar air.

As the air is breathed out of the nose during expiration, the first portion has the same composition as the room air, the last part of the dead space air is slightly mixed with the first part of the "effective ventilation." The last portion expired approaches in its composition the alveolar air.

If after an ordinary inspiration and expiration the individual continues to breathe out as much air as possible, he forces from the lungs the supplemental air which has the composition of the alveolar air. The first portion of this is mixed with the tidal air, the last portion can be used as a sample of the alveolar air. Even at the end of a forced expiration there is still a considerable amount of residual air in the lungs. All who are accustomed to making roentgen-ray examinations of the thorax are familiar with the great shrinkage of the lung when a pneumothorax forces all the air from the alveoli.

A forced inspiration will carry into the normal lungs a large amount of complemental air which tends to dilute the tidal air. With increased demands on the respiration, caused for instance by exercise, there is a partial utilization of both complemental and supplemental reserves and as a rule an increase in the rate of respiration. The total supplemental, tidal and complemental air is called the "vital capacity" and its measurement is becoming a matter of considerable clinical importance. The measurement is made quite easily by having the subject make the deepest possible inspiration and then breathe out into a spirometer, emptying the lungs as completely as possible. A few trials will demonstrate the greatest effort of which the individual is capable.

Normally the respiration is regular in its depth and rate and the average volume of air breathed per minute when the subject is quiet is 5 or 6 liters. With increasing demands for oxygen and the elimination of carbon dioxide the minute volume increases *pari passu*. This is necessary in order that the alveolar air may be maintained at a fairly constant composition. Under ordinary conditions this is remarkably uniform, but in diseases and a few other circumstances the alveolar air may contain an abnormally high or abnormally low percentage of carbon dioxide. The alveolar air is practically in gaseous equilibrium with the blood in the alveolar capillaries except in cardiac disease when the carbon dioxide content is distinctly lower than the blood, as has been shown by Peters and Barr.¹

This brings us to the phenomenon of "auspumpung"

¹ Peters and Barr: Jour. Biol. Chem., 1921, 45, 537.

which has played havoc with countless experiments on the basal metabolism and will continue to do so for years to come. Next to leaky apparatus, it has caused more trouble than any other factor. It has at times filled the literature with erroneous data and faulty conclusions most difficult to eradicate. The term originated in Germany and it does not seem to have any good English equivalent. It means a pumping out or washing out of carbon dioxide by over-ventilation of the lungs. If the effective minute volume is raised abnormally, either consciously or unconsciously, the lungs are ventilated with unusually fresh air into which there is an increased diffusion of carbon dioxide from the alveoli. This decrease in the percentage of CO_2 in the alveolar air causes an increased diffusion with consequent diminution of the gas in the blood. This in turn is followed by a decrease in all the tissues of the body. A surprisingly large amount of carbon dioxide is loosely combined in the body and is readily removed in a few minutes by "auspumpung." The oxygen stores of the body are not affected by moderate over-ventilation and this same increase in tidal air causes only a slight rise in the consumption of oxygen.

During brief periods of violent muscular exercise, however, a large amount of lactic acid may be formed and the body may go into debt for oxygen. In the recovery phase this "oxygen deficit" is repaid by the absorption of more oxygen than the patient is actually consuming.

Thus Soma Weiss¹ found that the washing out of CO_2 and the high respiratory quotient could last for more than fifteen minutes after starting work. A. V. Hill and his associates have shown that the R. Q. may rise to 1.5 or even 2.0 during the first ten to fifteen minutes of violent exercise. One-half hour later it will exhibit a compensatory fall to about 0.65. A depression may still be evident one and a half hours after the violent exercise is ended.

Henderson and Haggard² found that this blowing off of CO_2 and oxygen deficit were not very great in trained athletes. The reader is referred to their classical article in which they publish the results obtained on Yale oarsmen.

During the first few minutes of such over-ventilation, the CO_2 which is being excreted is greatly in excess of the amount being produced by the oxidative processes in the body. If the

¹ Weiss, S.: *Biochem. Ztschr.*, 1919, **101** 7; *Ibid.*, 1921, **121**, 40.

² Henderson and Haggard: *Am. Jour. of Physiol.*, 1925, **72**, 264.

respiratory quotient for this period is calculated $\left(\frac{\text{Vol. CO}_2}{\text{Vol. O}_2} \right)$ it will be high and all calculations based on this will be erroneous. The true respiratory quotient seldom rises above 1 except after a rich carbohydrate diet or in convalescence, but a review of the literature will show that many investigators have published respiratory quotients much above this level. Most of the experimenters who have published such quotients have been new at the game and when they try to explain the quotients the fat is indeed in the fire.

Fortunately, many of the calculations are based on the oxygen alone and as we have shown this is but little affected by "auspumpung." In fact, many of the modern types of apparatus devised by Benedict determine oxygen consumption only, thus side-stepping this source of error.

After the washing out of CO₂ by excessive ventilation there comes a period when equilibrium is established and the rate of the excretion of the gas really represents the rate at which it is being formed. This occurs, for instance, a few minutes after an individual starts the performance of some regular and uniform muscular exercise. When the increased ventilation stops for any reason there is naturally a reaccumulation of the stores of loosely combined CO₂ in the blood and tissues and for several minutes the excretion of the gas is much lower than the actual production. This makes the respiratory quotient appear low. This latter phase of irregular breathing is not found very often during the experimental periods and abnormally low quotients can usually be ascribed to leaky apparatus which makes the oxygen consumption appear much greater than it should be. Even in severe diabetes it is doubtful if the true quotient ever falls below 0.66 yet the literature is full of quotients of 0.60, 0.50 and even lower.

"Auspumpung" is caused by anything which augments the depth or rate of respiration, increasing the effective alveolar ventilation per minute. Deep breathing occurs in acidosis, in cardiac disease, in fever, etc., but in these conditions equilibrium is established and the CO₂ excretion is equal to the production. In Cheyne-Stokes respiration the excretion is obviously rhythmical. Such conditions cause no serious errors in experimental work, because they are easily detected. It is a reflex or nervous type of irregular breathing that is the real source of trouble. Respiration is seldom regular if the

individual becomes conscious of this function. Almost all untrained nervous subjects concentrate their attention on their breathing during the first part of a respiration experiment. The preparations for the test start the trouble, the introduction of the mouth piece augments it and the slight change in the smell and feeling of the air when the experimental period begins makes things still worse. By this time the breathing may be double its normal depth and the carbon dioxide is being washed out of the blood and tissues.

Some subjects will invariably show "auspumpung." These are fortunately great exceptions. Curiously enough they are not all of nervous temperament. Many individuals will cause trouble only during the first few tests. If the apparatus is a good one and the experimenter knows how to manage the patients there will be little or no trouble from this source. Inexperienced men learning the technic are the ones who encounter "auspumpung" and they usually fail to note its occurrence. It will save them much time and embarrassment if they invariably make a graphic record of the respiration.

This washing out of carbon dioxide affects only the short period types of apparatus. It seldom occurs in the large respiration chambers and does not alter the results in periods of one hour or longer.

The Internal Respiration.—The internal respiration takes place through the walls of the capillaries in the lungs and body tissues. These are so constituted that they furnish a maximum of surface and minimum of resistance to the diffusion of gases. In the lungs the blood is separated from the alveolar air by the thickness of one cell, only a few micra. As a result, the gases of the blood and of the alveoli come into equilibrium in the fraction of a second. Oxygen passes through the lining epithelium, through the serum into the hemoglobin of the red corpuscles. Carbon dioxide passes in the opposite direction, its removal from the hemoglobin being aided by the entrance of the oxygen. It has been recently shown that we can no longer consider the serum as the chief carrier of carbon dioxide. We have long known that serum carries but little oxygen.

When this arterial blood has been transported to the tissues the process is reversed, oxygen passes into the cells where the tension of this gas is low. Carbon dioxide which has been accumulating in the cells enters the hemoglobin helping to

drive out the oxygen. The final chemical reactions of the oxidation of proteins, fats and carbohydrates take place in the cells and perhaps to a certain extent in the lymph which bathes them.

The process of internal respiration is altered in certain pathological conditions. For instance, in some stages of pneumonia there may be a considerable amount of blood circulating through an unaërated lobe of a lung. When this returns to the heart it is mixed with the aërated blood. In some cases of pneumonia some of the hemoglobin is changed to methemoglobin which is inert as a carrier of oxygen. In patients with decompensated cardiac lesions Peters and Barr have shown many abnormalities of the internal respiration. There is a stasis of the circulation through the lungs and apparently some interference with the exchange of gases between blood and air. In order to effect this exchange it is necessary to provide the alveoli with air of a lower carbon dioxide content than in normals and there is an increased effective alveolar ventilation. Under such circumstances the low alveolar carbon dioxide does not indicate an acidosis because the CO_2 content and the CO_2 capacity of the pulmonary blood are normal or even above normal. In decompensated cardiac patients the circulation of blood is so slow that the cells show a marked lack of oxygen and accumulation of carbon dioxide. As a result, the hemoglobin is almost robbed of its oxygen and overloaded with carbon dioxide. Ordinarily the blood flowing from the forearm retains 75 per cent of its oxygen. In severe cardiac disease the oxygen saturation of the venous blood may fall to 18 per cent. This is the chief cause of cyanosis.

In severe anemia there is a great diminution in the capacity of the blood to carry oxygen and carbon dioxide. This is partially compensated by an increase in the circulation rate and perhaps the volume output of the heart but the chief factor is a more complete removal of the oxygen in the tissues so that there is abnormally high oxygen unsaturation of the venous blood just as in cardiac disease. In spite of this compensation, there is a sharp limit to the amount of muscular work that can be performed by patients with severe anemia. Carbon monoxide poisoning causes a loss of the oxygen combining power of part of the hemoglobin and the result is functionally the same as anemia.

The breathing of pure oxygen does not change the respira-

tory metabolism. A rise in the percentage of oxygen in the air breathed has but little effect in raising the amount of oxygen in arterial blood. Nevertheless, this slight rise may be of service in disease. Similarly, a considerable diminution of the oxygen percentage or vapor pressure has but little effect. The respiration is not doubled until the oxygen is at about one-third of its normal concentration. Men in good physical condition do not suffer serious effects until the oxygen has been reduced to about 7 per cent. This test has been used to determine the fitness of aviators.

Changes in the carbon dioxide content of the inspired air produce a more marked response. The respiration of normal men is doubled when the CO_2 rises to about 5 per cent. This increase in the ventilation of the lungs is necessary in order to maintain the alveolar air at its normal composition. When the inspired air contains 6 to 7 per cent CO_2 there is great respiratory distress. This phenomenon has been made of service in the clinic through the work of Peabody¹ and others.

Patients with cardiac disease respond by an abnormally rapid rise in the minute volume of respiration as the carbon dioxide of the inspired air is increased. Such tests are usually made by having the patient breathe back and forth into a spirometer meanwhile recording the volume of respiration.

We must not get false ideas of the effect of carbon dioxide from the writings of ventilating engineers. They use the percentage of this gas as an index of the contamination of the atmosphere of public buildings and consider the air very bad when the CO_2 rises from the normal of 0.03 per cent to 0.12 per cent. As a matter of fact, it is the humidity, heat and oppressive odors that makes crowded rooms uncomfortable. The writer has seen the crew of a submarine live and work in perfect health in an atmosphere of 2.5 per cent CO_2 during a four-day submergence.

Nitrogen gas, as far as metabolism is concerned, is absolutely inert. Under ordinary atmospheric pressure it is dissolved in the blood plasma according to its coefficient of solubility at body temperature. When the pressure is raised by submergence in a diving suit or in a caisson the percentage of nitrogen in the blood rises gradually and the gas in the tissues follows that in the blood. During a brief submergence the amount is so small that no symptoms follow a release of the pressure. After a prolonged submergence, especially at

¹ Peabody: *Arch. Int. Med.*, 1915, 16, 846.

high pressure, there are large amounts of nitrogen in solution in the blood and tissues and especially in the lipoids of the nervous system. Under such conditions a sudden removal of pressure makes it impossible for the gas to remain in solution and it forms bubbles in the tissues and bloodvessels just like those in a soda-water bottle when the cork is suddenly drawn. This produces caisson disease with excruciating pains throughout the body. If the sufferer is put back into a lock and the pressure reestablished the gas is dissolved once more and all the symptoms are relieved. The release of bubbles of nitrogen gas is prevented if the pressure is reduced gradually. Under such conditions the blood is able to carry the gas from the tissues to the lungs where it diffuses into the alveolar air with its diminished partial pressure of nitrogen. The whole trouble is due to the slow transportation of nitrogen gas.

The fact that nitrogen gas is inert in metabolism is of great importance in respiration experiments since it forms the basis of all calculations. Every experiment begins with a certain mixture of nitrogen, oxygen and carbon dioxide. At the end of the test we determine the changes in the oxygen and carbon dioxide and assume that the volume of nitrogen has not been changed by the respiration of the subject. We are justified in this assumption because under ordinary atmospheric conditions there is no reason to believe that the percentage of the gas in the blood could vary. Actual tests have shown no significant variation. If there were any accumulation of nitrogen or any utilization of nitrogen gas errors would be introduced in all respiration experiments. It would be impossible to obtain the wonderful agreement between the methods of direct and indirect calorimetry demonstrated so many years ago by Rubner, Atwater and Benedict and others. Of course this assumption would not be justified in experiments in which there are large variations of atmospheric pressure or in experiments on those leguminous plants which are able to fix the nitrogen of the air.

It is doubtful if any significant error is introduced in respiration experiments by the swallowing of air or the belching of gas from the stomach or the expulsion of flatus from the bowels. In a short observation it would be easy to detect any swallowing or belching serious enough to affect the results. Experiments on cattle and some laboratory animals are complicated by the excretion of methane which is formed in considerable quantities in the bowel.

CHAPTER V.

THE GENERAL PRINCIPLES OF RESPIRATION APPARATUS AND THE METHODS OF CALCULATION.

IN the preceding chapters we have reviewed enough of our physics, chemistry and physiology to enable us to work out many methods of determining the heat production of man. If we wished to use direct measurements we could follow the general principle of the bomb calorimeter, put the man in a metal chamber, immerse this in a measured amount of water and measure the temperature rise of the water. We should at the same time measure the water vaporized from the skin and lungs and calculate the heat lost in this fashion. Such an apparatus would be too bulky. We could more handily remove and measure the heat by letting a known amount of water flow through a cooling coil and determining how much its temperature was raised.

If we chose to measure the heat indirectly from the chemical reactions we could use either the carbon dioxide production or oxygen consumption or both together. The earliest clinical investigators used the carbon dioxide measurement because this was by all means the easiest. A man could breathe through a mouth piece or mask into a solution or reagent which would catch all the CO_2 or else he could be shut in a respiration chamber the exhaust air from which was passed through similar solutions. The process was simple but the CO_2 elimination in itself meant but little and a large error was sometimes introduced when they tried to find the calories from the carbon dioxide production. We have seen that 1 liter of carbon dioxide represents 5.047 calories when pure carbohydrate is used in the metabolism. When fat is oxidized the factor is raised to 6.694, a figure 33 per cent higher. Obviously, the error would be too large unless we were able to find out the relative amounts of fat and carbohydrate. Two or three hours after a meal rich in sugar or starch we could assume that 85 to 95 per cent of the calories

were being derived from carbohydrate. In the morning twelve or more hours after the last meal we might assume an average respiratory quotient of 0.82 with a calorific value of 5.88 for each liter of CO_2 . Benedict, Emmes and Riche¹ have shown that if the preceding meal were rich in carbohydrate, the average quotient may be 0.884 with a caloric value of 5.54 or about 6 per cent lower. Errors larger than this may be introduced in disease where we cannot approximate the respiratory quotient and huge errors may occur in short period experiments if there is any "auspumpung." We have seen how increasing the ventilation will wash CO_2 out of the blood and tissues. The writer² by breathing as deep and as fast as possible was able in a fifteen minute experiment to change his apparent respiratory quotient from 0.77 to 1.10 and a similar change was observed in a typhoid patient who unintentionally exhibited this phenomenon. These are rather extreme cases but an error of 5 or 10 per cent can be introduced without attracting the attention of the observer. We should not spend so much time on the possible errors of this old method if it were not being revived by King and Pearl.³ They have taken the figures obtained in long calorimeter observations to show the correlation between CO_2 and calories of heat production. In experiments in a respiratory chamber there is no tendency toward "auspumpung" and the fasting quotients usually fall between 0.80 and 0.88. This method also measures the CO_2 output of the skin which may be 1 to 2 per cent of the total. The writer has never had to exclude a calorimeter experiment on account of faulty measurement of carbon dioxide, but when in association with Dr. Warren Coleman he made several hundred ten-to fifteen-minute experiments on typhoid patients using the Benedict-unit apparatus about a third were excluded from publication because tracings showed that the respiration was irregular.

There is a method, that employed by Pettenkofer and Voit, which requires the determination of carbon dioxide and water elimination over a period about a day long. If the subject is weighed at the start of the experiment and the weight of all his food and drink added, this sum plus his

¹ Benedict, Emmes and Riche: *Am. Jour. Physiol.*, 1911, 27, 383.

² Coleman and Du Bois: *Arch. Int. Med.*, 1914, 14, 168.

³ King: *Johns Hopkins Hosp. Bull.*, 1921, 32, 277; 1923, 34, 304 and 349.

oxygen absorption should exactly equal the sum of his weight at the end of the experiment, his carbon dioxide and water excretion plus urine and feces passed during the test period. Knowing the carbon dioxide excretion and oxygen consumption we can estimate the total metabolism.

Another method gives us the approximate calories if we know the carbon dioxide production for the period of a day and know also the carbon and nitrogen content of the food and the excreta. We assume, not any too correctly, that the carbohydrate of the food is all oxidized the day it is ingested. We calculate the protein metabolism from the nitrogen of the urine. We can then determine how much carbon is derived from these and subtract the sum from the total carbon. This leaves the carbon derived from the metabolism of the fat and we can therefore calculate the grams of all three substances metabolized. This method has been used with the Pettenkofer-Voit chamber.

It is obviously impossible for a subject to remain perfectly quiet for a whole day and experiments of this length never comply with the conditions now considered "basal." They do, however, give a good idea of the total requirements for the day with the effects of food and moderate activity.

Most of the machines now in use measure the oxygen consumption only depending on the fact that there is little difference between the calorific factors for a liter of oxygen used in the combustion of these three different foodstuffs. The factors are as follows:

TABLE II.—CALORIFIC VALUE OF 1 L.O₂.

Carbohydrate	5.047
Fat	4.686
Protein	4.485
For average person fasting twelve to fourteen hours, R. Q., .82	4.8

If we therefore measure accurately the oxygen consumption we can estimate the calories with a maximum error of 3.5 per cent. This maximum would be approached in experiments after food unless the factor were changed according to the probable amounts of the various foods metabolized. In observations made twelve to fourteen hours after the last meal the error will seldom be greater than 2 per cent if the average figure for a quotient of 0.82 is used. Such errors in a large series of tests will fall partly on the plus side and partly

on the minus, thus tending to neutralize each other. There is, however, a constant plus error of about 1 per cent if calculations are based on the table of Zuntz and Schumburg which gives the values for the non-protein respiratory quotient. If we derive 15 per cent of the calories from protein, and this is a fair average figure, the calorific value of a liter of oxygen is 1 per cent lower than the Zuntz and Schumburg figure.

Most of the errors of calculation can be removed if the oxygen consumption and carbon dioxide excretion have been measured in a respiration chamber or Tissot spirometer and the nitrogen excretion determined for the experimental period. This gives us for the normal subject all the factors necessary for the calculations under all possible combinations of foodstuffs unless alcohol or other unusual foods are given. In disease and especially diabetes, as we shall see later, it is also necessary to know the amounts of glucose and ketones in the urine.

In the preceding pages we have shown that the urinary nitrogen in a given period tells us the level of the protein metabolism. Certain precautions must be taken in regard to collecting a specimen of urine for this purpose. In the first place, we must be sure that the kidneys are normal enough to excrete urea promptly and that there is no reason to suspect a low phenolsulphonephthalein test or high non-protein nitrogen of the blood. We must be sure that the bladder is completely emptied at each voiding and that there is a sufficiently large enough supply of water so that there are no great changes in the concentration of urine. Some gifted subjects can void quantitatively every hour precisely on the desired second. Most people cannot do so much oftener than once every two hours and with untrained or nervous subjects you may have to go four hours between specimens. Periods of one hour are a little too short to give a true curve of nitrogen excretion except in unusual cases. Two-hour periods are usually the best but we must remember that an error can be caused by the loss of a few drops of urine or by a slight mistake in the time. A four-hour period will give a fairly close idea of the protein metabolism which is usually rather constant except after meals containing considerable amounts of meat.

Knowing the nitrogen excretion we multiply this figure by the following factors:

1 gm. urinary nitrogen represents:

Calories derived from protein	26.51 cal.
CO ₂ derived from protein	9.35 gm.
O ₂ consumed in metabolism of protein	8.45 gm.

We already have determined the total CO₂ and O₂ in a given experimental period. The above factors make it possible for us to find the grams of CO₂ and O₂ assignable to the protein and subtract from the totals. This leaves the non-protein CO₂ and O₂ and by dividing the volume of the former by the volume of the latter we obtain the non-protein respiratory quotient. Referring to the table prepared by Zuntz and Schumburg¹ and modified recently by Lusk² we note the calorific value of a liter of oxygen for this quotient and also the relative percentage of the non-protein calories derived from fat and carbohydrate. We can then multiply the liters of non-protein oxygen by this factor and find the total non-protein calories. If we multiply this figure by the percentage derived from fat we can, of course, obtain the exact number of fat calories and carbohydrate calories. We have already found the protein calories so we can add all three together and find the total heat production.

TABLE 12.—SAMPLE CALCULATION.

NAME <i>W. H. O.</i>	DATE <i>April 7, 1917</i>	EXP. NO. <i>358</i>
Urinary nitrogen	0.3895 Grams per hour	
Total CO ₂ excretion	21.73 Grams per hour	
Total O ₂ consumption	19.84 Grams per hour	
Protein calories	0.3895 × 26.51 = 10.33 Calories	
Protein CO ₂	0.3895 × 9.35 = 3.64 Grams	
Protein O ₂	0.3895 × 8.45 = 3.29 Grams	
Total CO ₂ . . . 21.73	Total O ₂ 19.84	
Protein CO ₂ . . . 3.64	Protein O ₂ 3.29	
Non-protein CO ₂ 18.09	Non-protein O ₂ . . 16.55	

Changing grams to liters using factors given on page 57, Table 9.

$$18.09 \times 0.5089 = \frac{9.20 \text{ Liters CO}_2}{0.795 \text{ Non-protein respiratory quotient}} = 0.795 \text{ Non-protein respiratory quotient}$$

$$16.55 \times 0.6997 = 11.58 \text{ Liters O}_2$$

¹ Zuntz and Schumburg: *Physiologie des Menschen*, Berlin, 1901.

² Lusk: *Jour. Biol. Chem.*, 1924, **59**, 41.

When the non-protein R. Q. is 0.795 each liter of non-protein oxygen represents 4.795 calories and of these calories 31.7 per cent is derived from carbohydrate and 68.3 per cent from fat. (Table 3, page 39.)

11.58	×	4.795	=	55.52	Non-protein calories
55.52	×	0.317	=	17.60	Calories from carbohydrate
55.52	×	0.683	=	37.92	Calories from fat
0.3895	×	26.51	=	10.33	Calories from protein
					<hr/>
					65.85 Total calories.

The calculation given on p. 71 is not difficult but it is not much used except by the Department of Physiology of the Cornell Medical College and by the Russell Sage Institute of Pathology in New York. Some investigators make use of the valuable short cut of Magnus-Levy¹ who realized that in most respiration experiments begun twelve to fourteen hours after the last meal the protein furnished 12 to 18 per cent of the total calories. He, therefore, made a table of calorific values of oxygen based on the assumption that protein furnished 15 per cent of the calories.

An accurate and rapid method of calculating the calorific value of a liter of oxygen was devised by a medical student, the late Alfred M. Michaelis.² He found the percentage of oxygen used in the metabolism of protein by dividing the nitrogen of the urine voided during a given period by the total oxygen consumed during the same period. Knowing this and the respiratory quotient, one can locate on the triangle the exact calorific value of a liter of oxygen. This allows us to determine the total calories. On his second triangle, using the same factor of $\frac{N_2}{O_2}$, we can obtain the percentage of calories from protein, carbohydrate and fat.

There is a crude method of estimating heat production by measuring the food and its calories, either estimating or analyzing the fecal losses. If the individuals examined remain in weight and nitrogen balance it is assumed that they have been receiving exactly as many calories as they have produced. This method is of some utility in dealing with large masses

¹ Michaelis: Jour. Biol. Chem., 1924, 59, 51.

² Magnus-Levy: Von Noorden's Handbuch., 1901, I, 192.

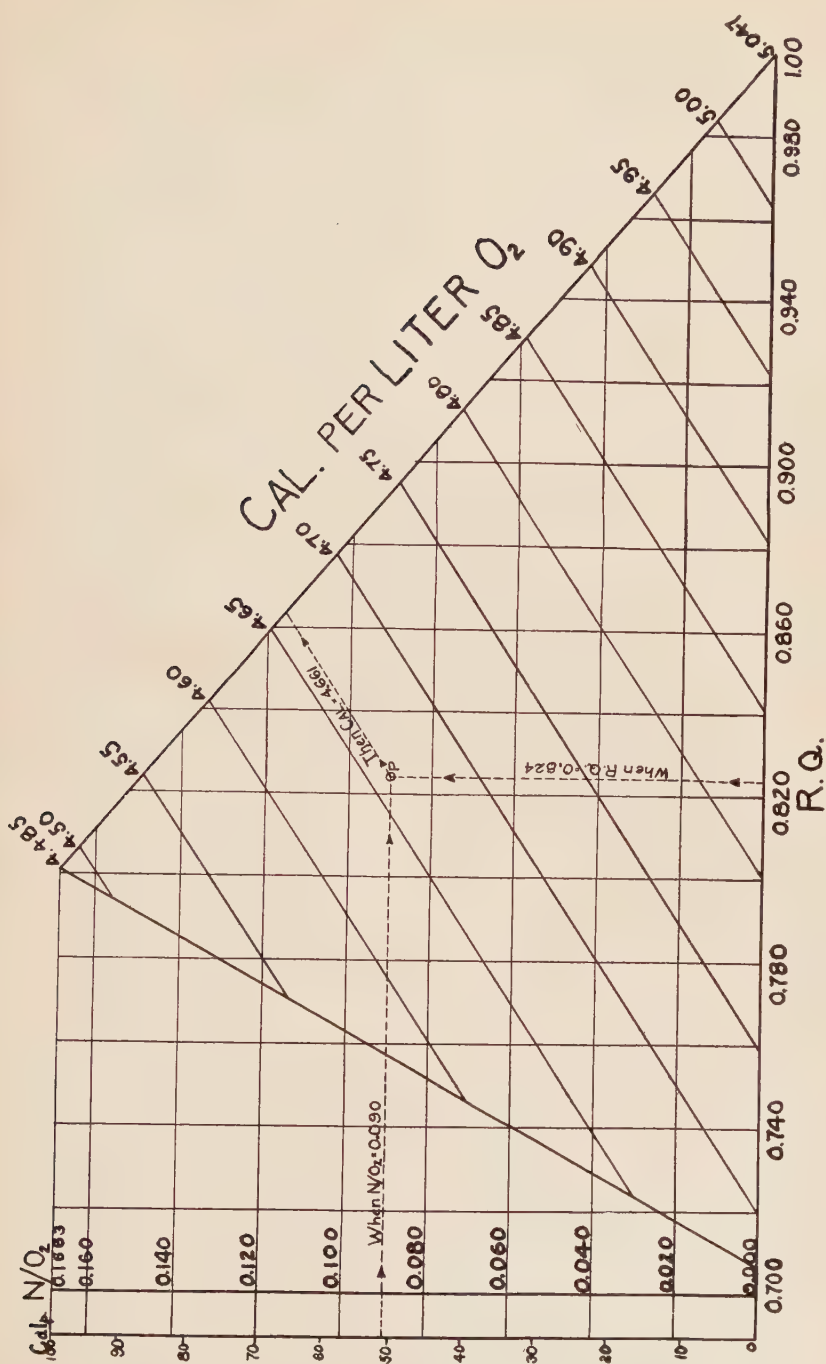


FIG. 7.—Chart showing the calorific value of a liter of oxygen according to the total $R.Q.$ and the relationship of urinary nitrogen and total oxygen consumption. (From Michaelis.)

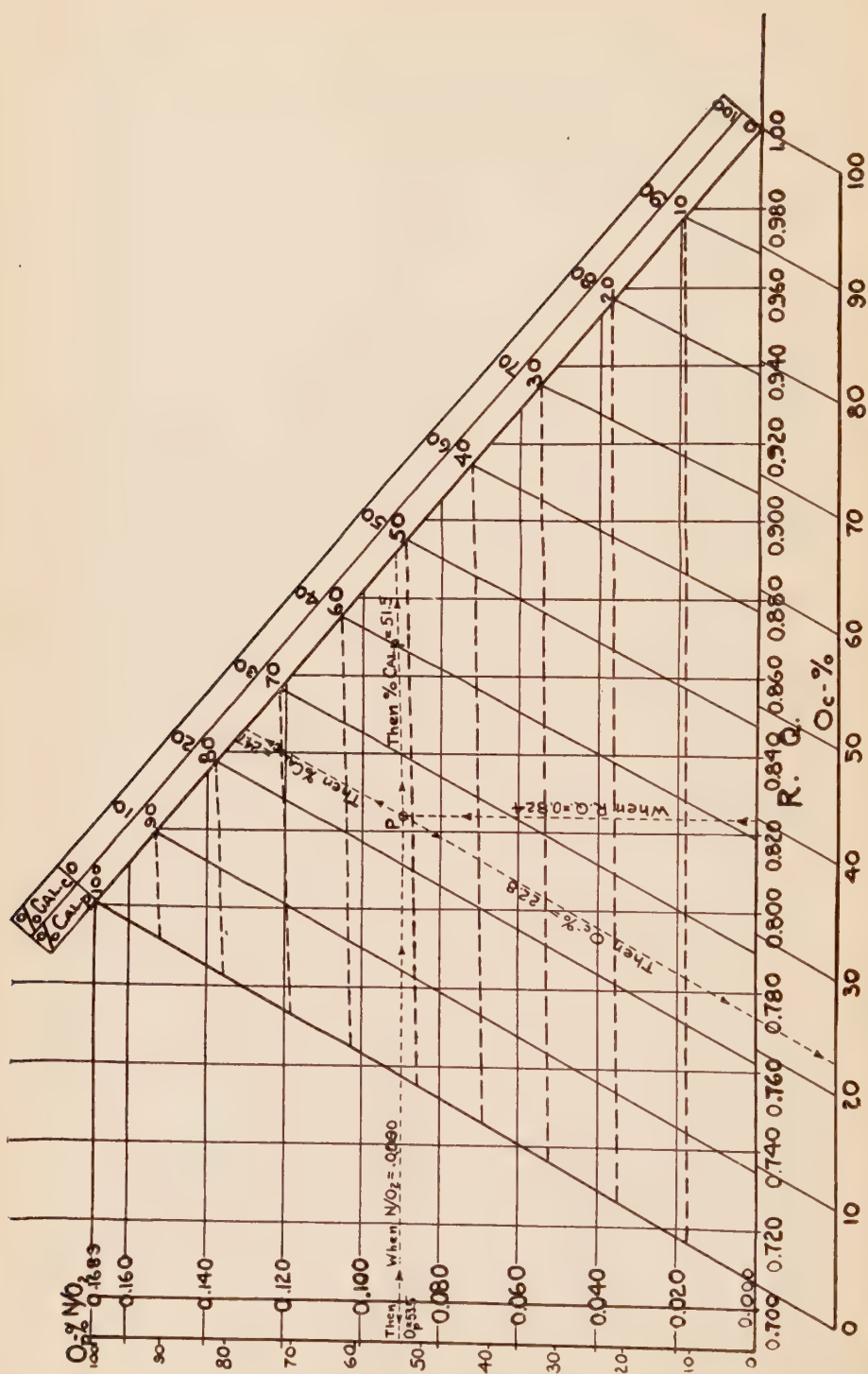


FIG. 8.—Chart to give the percentage of calories from protein and carbohydrate and percentage of oxygen used in oxidation of each.

of normal people, but it is not adapted to the study of disease. In the first place, it gives us the total metabolism and not the basal. In the second place, it is founded on the assumption that weight and nitrogen balance mean nutritive balance. This does not hold in disease and cannot even be relied upon in health unless long periods of experimentation are used.

CALORIMETERS AND RESPIRATION APPARATUS.

It is not desirable or possible in a book of this size to describe at length all the important forms of apparatus used in determining the respiratory exchange. No one is much interested in technic unless he is actively engaged in the work and even then he is interested chiefly in one type of apparatus. Such a man should consult the original sources and devour every scrap of information about his machine that has ever been published.

The average reader is wearied by details but should be interested in the general principles of the various devices which have furnished us with out knowledge of basal metabolism. He should know the advantages and limitations of each type since these modify our interpretation of the results. We still use many experiments which are not ideal from a technical standpoint. We cannot neglect the historical background which modifies profoundly the popular conceptions of the subject. The man who does not know something about the workers of the last fifty years is in great danger of repeating many of their errors. He also wastes much time by inventing "improvements" which were tried and discarded in previous generations.

In addition to the original articles in which the various types of respiration apparatus are described in detail there are several more comprehensive discussions of the subject. The reader is referred to the reviews by Johansson,¹ Jaquet,² Tigerstedt,³ Loewy⁴ and the more recent works of Carpenter⁵

¹ Johansson: *Aberhalden's Handbuch der Biochem. Arbeitsmethoden*, Berlin u. Wien, 1910, 3,² 1114-1170.

² Jaquet: *Ergeb. der Physiol.*, 1903, 2,¹ 457.

³ Tigerstedt: *Handbuch der physiol. Methodik*, Leipzig, 1911, 1, Part III, 70.

⁴ Loewy: *Oppenheimer's Handbuch der Biochem.*, 1911, 4,¹ 133.

⁵ Carpenter: *Carnegie Institution of Washington Publication No. 216*, 1915.

and Murlin.¹ Carpenter has compared the results obtained with six different machines and has described the technic of each in an excellent monograph. Boothby and Sandiford² have described in great detail the technic of the Tissot method which is so extensively used in this country and F. G. Benedict^{3,4} has given a comprehensive account of all the various types of respiration apparatus developed in the Nutrition Laboratory of Boston.

The Measurement of Heat by Direct Calorimetry.—The principles of direct calorimetry are best illustrated by the bomb calorimeter. This is used to determine the heat of combustion of various foods and fuels and all our calculations are based on its findings. The simplest type of this apparatus is the one developed by Riche⁵ in Lusk's laboratory.

The Riche Bomb Calorimeter.—This consists of a strong steel cylinder with a screw cap which contains a weighed amount of the powdered food being tested. The bomb is filled with oxygen at about 25-atmospheres pressure and then immersed in a measured amount of water placed in a large vacuum cup. After a few minutes the bomb and water have reached thermal equilibrium and the temperature of the water is read on a delicate thermometer. By means of an electric current a platinum wire just over the food is made red hot. This ignites a small linen thread which drops into the powder causing a combustion which is instantaneous on account of the high pressure of oxygen. There is a rapid rise in the temperature of the bomb and surrounding water. Knowing the weight of the water and the hydrothermal equivalent of the bomb we may calculate the calories of the combustion. One small calory is the amount of heat required to raise 1 gram of distilled water 1° C. For all metabolism work we use the large calory which is 1000 times as great.

The hydrothermal equivalent of the bomb is the water equivalent of the bomb from a thermal standpoint. Steel

¹ Murlin: *Abt's Pediatrics*, Philadelphia, W. B. Saunders Company, 1923, p. 520.

² Boothby and Sandiford: *Laboratory Manual of the Technic of Basal Metabolic Rate Determinations*, Philadelphia, W. B. Saunders Company, 1920.

³ Benedict, F. G.: *Methoden zur Bestimmung des Gaswechsels bei Tieren und Menschen*, Abderhalden's *Handbuch der biol. Arbeitsmeth.*, 1924, Abt. 4, Teil 10, 415.

⁴ Benedict: *Boston Med. and Surg. Jour.*, 1925, **193**, 583 and 807.

⁵ Riche: *Jour. Am. Chem. Soc.*, 1913, **35**, 1747.

has a low specific heat and it is much easier to warm up a kilogram of this substance than a kilogram of water. This matter of the water equivalents of containers is of considerable importance in all direct calorimeters. When we come to the mechanism of the rise and fall of the body temperature we shall have to study in detail the hydrothermal equivalent of the human body which can store or lose a considerable amount of heat.

Benedict and Fox¹ have devised a simple and inexpensive oxy-calorimeter which can be used for the combustion of dried food or feces. A glass combustion chamber is attached to a Benedict portable or Benedict-student apparatus (see pp. 97, 102) and the oxygen consumed in burning the sample is measured directly. The calorific values of a liter of oxygen for the different foods all lie between 4.68 and 5.0 and the actual error of calculation is small since the composition of the mixture is usually known with considerable accuracy. This new device should be of great service in every metabolism laboratory though its greatest service will perhaps be in fuel analysis.

Respiration Calorimeters.—*Direct Calorimetry.*—In most respiration calorimeters the heat is removed by a stream of water flowing through pipes in the chamber. Knowing the amount of water which has flowed through the apparatus and the temperature before and after passing through the pipes it is possible to determine the calories removed in this fashion. To this must be added the heat dissipated in the vaporization of water.

In order to calculate the amount of water vaporized, we must be able to analyze the water in the air. This is usually accomplished by passing the air through a weighing bottle filled with granules of calcium chloride or strong sulphuric acid or sulphuric acid on cracked pumice stone. Some prefer to use a psychrometer consisting of wet and dry bulb thermometers, thus making a reading of the humidity. These methods will give with great accuracy the amount of water removed from the chamber or remaining suspended in the air of the chamber but there is no method of determining the amount of water vapor contained in the clothing or on the walls of the calorimeter. Fortunately, this does not affect

¹ Benedict and Fox: *Industrial and Engineering Chemistry*, 1925, **17**, 912; *Jour. of Biol. Chem.*, 1925, **66**, 783.

the direct calorimetry since all the heat abstracted by this water during vaporization is released during its condensation.

Air Analysis.—The analysis of carbon dioxide and oxygen is of principal importance in the methods of indirect calorimetry. The simplest apparatus is the old Orsat in which a sample of the gas mixture is collected in a burette over water or mercury. This is then passed into a solution of sodium or potassium hydroxide which absorbs all the carbon dioxide. It is returned to the burette and measured to determine the loss of volume. Next it is thoroughly exposed to a solution of potassium pyrogallate which slowly absorbs the oxygen. Again the shrinkage is measured to determine the percentage of this gas. Nitrogen is not absorbed by either solution.

Numerous modifications of this Orsat apparatus are in vogue. The Sondén-Pettersson¹ is the most accurate but it is extremely fragile and few have mastered its technic. The Haldane² apparatus is the most popular being accurate and compact but it has many stop-cocks which cause trouble. A good technician can master it in a month. The new Henderson³ apparatus with a few minor improvements is just as accurate as the Haldane and so much simpler that it will doubtless become the favorite type. Carpenter⁴ has recently devised an apparatus of great accuracy which will be of service when the changes in the composition of the air are very small. Carbon dioxide in large amounts can be removed from a current of air by means of a bottle filled with a mixture of caustic soda and lime called soda-lime⁵ which is by all odds

¹ Sondén-Pettersson: See description in Benedict, Carnegie Institution of Washington Publication No. 166, 1912.

² Haldane: *Methods of Air Analysis*, London, Griffin & Co., 1912.

³ Henderson, Y.: *Jour. Biol. Chem.*, 1918, **33**, 31.

⁴ Carpenter: *Jour. Metab. Res.*, July-August, 1923, vol. 4.

⁵ "750 grams of unslaked lime and 750 grams of crude commercial sodium hydroxide are each weighed separately. The caustic soda is dissolved in 450 cc of water in an iron pot over a gas flame. When this is thoroughly dissolved the lime, which has been previously pulverized, is carefully but rapidly sifted into the pot, the flame turned down and the whole mass thoroughly stirred *with a long-handled iron rod* until slaking is completed. The finished material should be lumpy and slightly moist to the touch, but not so moist as to be sticky nor so dry as to be powdered easily. After cooling, the material is broken into sizes suitable for use. We have found for this purpose that material which passes through a sieve with a mesh of 4 mm. is best." (Benedict.) This is the original type of soda-lime and it may now be obtained from various commercial houses or from the dealers in respiration apparatus. The new Navy (Wilson) type of soda-lime is too moist for calorimeter chambers but is well adapted to the smaller machines.

the best substance available for this purpose. Sodium hydroxide in granules or in solution can be used. Samples of air can be analyzed for CO_2 by passing a measured amount through U-tubes filled with granules of soda-lime.

Using these various principles for the measurement of heat and the gases of respiration many varieties of apparatus have been devised. They may be divided into two main groups: (1) The respiration chambers which enclose the whole subject. (2) The smaller types of apparatus to which the patient is attached by means of mouth pieces, nose pieces or masks. This second type is much smaller, cheaper and often easier to operate than the chamber type. It employs periods of six to fifteen minutes instead of two to ten hours. Naturally, it lends itself well to clinical purposes and is much more popular than its bulkier competitor which, however, will always be indispensable in certain research problems.

All of the small types and most respiration chambers depend entirely upon the method of indirect calorimetry. It is hardly proper to call them calorimeters and general usage designates them as respiration apparatus. The term calorimeter should be reserved for those respiration chambers which use the physical methods of direct calorimetry in addition to the chemical methods of indirect calorimetry.

Respiration Chambers.—*The Pettenkofer-Voit Chamber.*¹—This apparatus was devised in 1862 and duplicates of the original are still in use at the present time. Carl Voit, the physiologist, took his problem to Pettenkofer, the physicist. The latter devised an air-tight chamber large enough to hold a bed and chair, ventilated by a large gas meter which measured the air passing through this box. Smaller meters withdrew continuous samples of the ingoing and outgoing air. These were passed through weighing bottles filled with cracked pumice stone soaked in sulphuric acid and through long tubes containing barium hydroxide. This latter caught and measured the CO_2 . Before an experiment, the subject was weighed and a careful record was kept of the weight of his ingesta and its carbon and nitrogen content. In a similar fashion, the excreta were weighed and analyzed for carbon and nitrogen. In this manner it was possible to determine just how many grams of these two elements were retained in or lost from the body. The oxygen consumption was measured by an indirect

¹ Pettenkofer: Ann. d. Chem. u. Pharmazie, 1862, Suppl. 2, 1.

method. To the weight of the patient at the beginning of the observation was added the weight of all the ingesta. This was subtracted from the weight of the patient at the end of the experiment plus the weight of all the excreta including the carbon dioxide and water of vaporization. The difference between these two sums is due to the oxygen which has been absorbed.

Knowing the carbon dioxide production, the oxygen consumption and the nitrogen of the urine it was possible to calculate the grams of protein and fat consumed and make a rough estimate of the carbohydrate utilized. The nitrogen of the urine indicated the amount of oxygen consumed and carbon dioxide produced in the metabolism of protein. The remainder could, therefore, be allotted to carbohydrate and fat. In a starvation experiment Voit assumed that the glycogen stores would play a negligible part. This is not true since Benedict has shown that as much as 180 grams may be oxidized during the first day of starvation. When Voit administered food during the experimental period, he assumed that the carbohydrates were oxidized within a few hours. This is usually but not always true since the glycogen stores may be increased or decreased and there may even be a transformation of carbohydrate into fat.

In spite of these possible errors the work of Pettenkofer and Voit was surprisingly accurate when we consider the difficulty in measuring the water of vaporization. There was another and more serious error when it came to measuring the basal metabolism. In a large respiration chamber with long experimental periods it is almost impossible for a person to remain at absolute rest. Most of the investigators who have used the Pettenkofer-Voit chamber have studied subjects who slept during the night and observed the condition called "Zimmerruhe" during the day. "Quiet in a room" permits sitting in a chair, dressing, reading, eating, etc., and may require 15 to 50 per cent more calories than the absolute muscular relaxation required in modern basal determinations. The whole school which followed Voit never seemed to realize this. The writer himself¹ fell into this error as late as 1909 when studying diabetic patients in this type of chamber. The results were of some value, however,

¹ Du Bois and Veeder: *Arch. Int. Med.*, 1910, 5, 37.

because he, himself, served as normal control and duplicated carefully the activity of the patients. On this occasion his metabolism was 32 per cent higher than his basal figures as determined in a calorimeter four years later.

Rubner's Dog Calorimeter.—Rubner,¹ a pupil of Voit, performed most of his experiments on man in a Pettenkofer-Voit chamber. For his classical dog experiments he constructed the first true respiration calorimeter combining the direct measurement of heat with the chemical analysis of the air according to the methods of Pettenkofer. Rubner measured the heat by determining the rise in temperature of the air as it passed through the chamber which was carefully insulated from heat loss to the surrounding room by means of a water jacket. Using this apparatus Rubner was the first to prove that the methods of direct and indirect calorimetry agreed closely, thus applying to animal experimentation the law of the conservation of energy.

Rubner's work was fundamental and invaluable but its service in establishing figures for the basal metabolism was somewhat marred by the unknown degree of activity of the experimental animals. It was not possible to keep an accurate record of all muscular movements and exclude all experiments in which the animal was restless. If one of Rubner's dogs had scratched fleas during an observation our knowledge of some of the laws of metabolism would have been postponed many years. The metabolism of one dog plus one flea may be double that of the two measured separately.

The Atwater - Rosa - Benedict Respiration Calorimeter.—Atwater, an American who had studied with Voit, began the construction of a respiration calorimeter for man at about the same time that Rubner was working on a similar apparatus for dogs. Aided by funds from the United States Government and by the active coöperation of an able physicist, Rosa,² an apparatus was constructed which measured the water and carbon dioxide output very much after the manner of Pettenkofer and determined the heat by recording the temperature of a stream of water as it flowed into and out of a system of pipes in the calorimeter. At a later date,

¹ Rubner: *Kalorimetrie in Tigerstedt's Handbuch der physiol. Methodik*, 1911, I, Part 3, 150.

² Atwater and Rosa: *Report of the Storrs Agricul. Exper. Stations*, 1897, p. 212.

largely through the ingenuity of F. G. Benedict,¹ the closed circuit principle was made applicable so that the same air was used over and over again and the oxygen consumption measured directly.

Since that time numerous improvements have been made in Benedict's Nutrition Laboratory in Boston² and in Lusk's laboratory by Williams³ and Riche and Soderstrom.⁴ The latest calorimeter is that of the Russell Sage Institute of Pathology in Bellevue Hospital, New York (Frontispiece). This has been unusually well described by Lusk⁵ and his summary is herewith repeated *verbatim*:

Principle of the Atwater-Rosa-Benedict Respiration Calorimeter.—"The apparatus is divided into two functional parts, one for measuring the gaseous exchange, the other for measuring the heat production of the subject. A schematic presentation is here given (Fig. 9).

The Gas Analysis.—The inner lining of the apparatus presents an air-tight copper box having a capacity of 1123 liters. One end of the box, through which the patient lying on the bed is admitted, may be closed with a glass plate by means of wax. The air within the box is purified by drawing it out of an opening in the box through a rubber tube and forcing it by means of a rotary blower through a system of *absorbers*, whence it returns to the box by another rubber tube. It passes (see diagram) first through sulphuric acid (1), which removes the water, then through moist soda-lime (2), which removes the carbon dioxide and next through sulphuric acid (3), which absorbs the moisture taken from the soda-lime. If the bottles be previously weighed, the gain in weight of 1 represents water absorbed, and the gain in weight of 2 + 3 equals the carbon dioxide absorbed. By this method the water and carbon dioxide produced by a man are taken from the air, while oxygen within the chamber is being absorbed by the man himself. This causes a diminution in the volume of the contents of the box. In order to replace the oxygen used, oxygen is automatically fed into the system from an oxygen

¹ Atwater and Benedict: Carnegie Institution of Washington Publication No. 42, 1905.

² Benedict and Carpenter: Carnegie Institution of Washington Publication No. 123, 1910.

³ Williams: Jour. Biol. Chem., 1912, 12, 317.

⁴ Riche and Soderstrom: Clin. Cal. 2, Arch. Int. Med., 1915, 15, 805.

⁵ Lusk: Clin. Cal. 1, Arch. Int. Med., 1915, 15, 793.

cylinder which may be weighed before and after the period. The automatic feeding of oxygen into the box is accomplished by means of a spirometer whose interior is connected with the interior of the calorimeter chamber. As the volume of

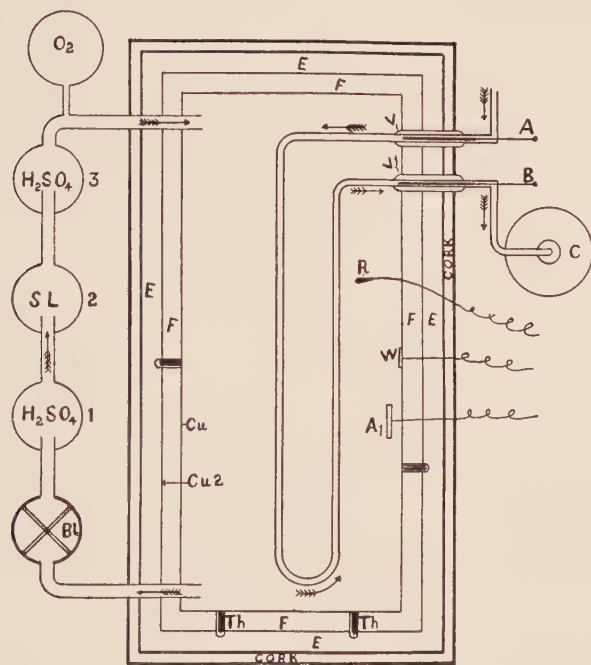


FIG. 9.—Schematic diagram of the Atwater-Rosa-Benedict respiration calorimeter.

Ventilating system: O_2 , oxygen introduced as consumed by subject; 3, H_2SO_4 to catch moisture given off by soda-lime; 2, soda-lime to remove CO_2 ; 1, H_2SO_4 to remove moisture given off by patient; Bl., blower to keep air in circulation.

Indirect calorimetry: Increase in weight of H_2SO_4 (1) = water elimination of subject; increase in weight of soda-lime (2) + increase on weight of H_2SO_4 , (3) = CO_2 elimination; decrease in weight of oxygen tank = oxygen consumption of subject.

Heat-absorbing system: A, thermometer to record temperature of ingoing water; B, thermometer to record temperature of outgoing water; V, vacuum jacket; C, tank for weighing water which has passed through calorimeter each hour; W, thermometer for measuring temperature of wall; A₁, thermometer for measuring temperature of the air; R, rectal thermometer for measuring temperature of subject.

Direct calorimetry: Average difference of A and B \times liters of water + (gm. water eliminated \times 0.586) + (change in temperature of wall \times hydrothermal equivalent of box) + (change of temperature of body \times hydrothermal equivalent of body) = total calories produced.

Th, thermocouple; Cu, inner copper wall; Cu₂, outer copper wall; E, F, dead air spaces.

the air in the box decreases, the spirometer falls until a certain point is reached, at which an electric contact releases a clamp, which allows oxygen from the oxygen cylinder to enter the box, causing the spirometer to rise, break its electric contact and clamp off the oxygen supply. So sensitive is the spirometer to the movement of the patient that a device called a 'work adder' has been attached to it, which records the subject's movements.

"At the beginning of an hourly period of experimentation an observer at the table calls 'time.' At this instant the rotary blower is stopped, the air current switched so as to pass through a new set of weighed absorbers and then the rotary blower is started again. At the word 'time' an operator also turns a pet-cock which cuts off the respiratory chamber from the spirometer cylinder, which is then filled, always to a given point, with oxygen from the oxygen cylinder. The pet-cock is now opened and a freshly weighed oxygen cylinder is placed in the position of the other, which is removed. Repeating these procedures an hour later, one may determine by difference in weight the gain of water and carbon dioxide by the absorbers and the loss of oxygen by the cylinder. The figures are subject to corrections due to (1) gain or loss of water or carbon dioxide content in the box itself, during the period, which gain or loss must be added to or subtracted from the increase in weight of the absorber system. This gain or loss of water and carbon dioxide in the box also affects the volume of the air in the box and, therefore, the quantity of oxygen admitted, as do, in addition (2), a change in temperature within the box and (3) a change in barometric pressure. These corrections must be made in order to determine whether oxygen is to be added or subtracted from the quantity which has been furnished from the oxygen cylinder. The result gives the quantity of oxygen which the man has absorbed. It is apparent that all the errors of determination fall on the oxygen, and yet the exactness of the method is witnessed by the close approximation in alcohol check experiments of the theoretical and actual values for oxygen consumed.

"If a person in the calorimeter moves even the arm during the critical moments just before 'time' is called, the increased local heating of the air may cause the spirometer to rise to a considerable height, of which the air thermometers inside the

box fail to make compensatory record, and the oxygen determination will be too low in that hour and too high in the next.

"Analysis of the air in the interior of the chamber is made just before the beginning of each hour by passing 10 liters of air from the box through 3 U-tubes containing, respectively, sulphuric acid, soda-lime and sulphuric acid, then through a Bohr gas meter and back into the box again. This is called the 'residual analysis.'

"Under the conditions present in the respiration apparatus, carbon dioxide is measured with the greatest ease and accuracy. Oxygen is also measured with accuracy if the person within the box lies perfectly quiet for ten minutes before the end of the period, whereas water production is the least accurate of all the determinations, on account of the varying hygroscopic condition of the walls, bedding and other surfaces within the closed spaces of the apparatus.

"*The Measurement of Heat Produced.*—Roughly speaking, one-quarter of the heat eliminated by a man is present in the water vapor which is absorbed by the first sulphuric acid bottle on the absorber table. At 20° C. 0.586 calories are contained as latent heat in 1 gram of vaporized water.

"The rest of the heat loss takes place by radiation and conduction. It is this heat which is measured by the calorimeter, itself. The mechanism of the calorimeter is essentially two-fold. In the first place there is no heat loss through the walls of the apparatus, and, second, the heat produced by a man within is removed from the chamber by a current of cold water flowing through copper tubes suspended from the upper wall of the chamber. If the walls allowed no heat to pass, it is obvious that without the cooling effect of the water-pipes the temperature of the air in the box would soon attain the temperature of the human body instead of being about 23° C., at which it is usually held. The apparatus is therefore a constant-temperature, water-cooled calorimeter. It is evident that if no heat is allowed to pass through the walls of the calorimeter, then the heat produced within the chamber will be removed in the current of cold water flowing through the heat-absorbing pipes inside the chamber of the apparatus. If the temperatures of the ingoing and of the outgoing water are known and the quantity of water which has passed through the heat-absorber during an hour is measured, the quantity of heat carried away in the current of water can be accurately

determined. For example, if the difference between the temperature of the ingoing and outgoing water is 2.5°C , and 20 liters of water have passed through the heat absorber in one hour, then 50 calories of heat have been carried away from the apparatus during the period. If the temperature of the walls within the apparatus has undergone a change this value is subject to corrections, but otherwise the total heat elimination of the person is measured by the 50 calories so determined plus the heat value of water vaporized during the hour.

"To obtain an even flow of water through the heat-absorber the water is supplied from a constant-level tank placed above the calorimeter. To obtain ingoing water of an even temperature, Williams passed the previously ice-cooled water current through a Gouy temperature regulator and then through a current regulator designed by himself. These improvements allow the ingoing water to enter the calorimeter at a temperature which may not vary more than 0.02°C . during hours of experimentation and, for the first time, permit the exact measurement of small quantities of heat in this type of apparatus. The temperatures of the ingoing and outgoing water are taken every four minutes by electrical resistance thermometers and are read in connection with a galvanometer and Kohlrausch bridge on an observer's table. The quantity of the water-flow is determined by weighing; the water is diverted at the call of 'time,' so that the exact quantity for the hour is collected in a previously weighed receptacle.

"Having learned how the heat produced within the apparatus is carried away, the problem of how to prevent loss of heat through the walls of the chamber remains to be discussed. This was accomplished through a device introduced by Rosa. The calorimeter is constructed of three walls, an inner copper wall which has already been described as the lining of the respiration chamber, an outer copper wall separated from the inner wall by a space of dead air, and an insulating wall (made of two layers of 'compo-board,' the space between them being filled with cork), which insulating wall is separated from the outer copper wall by a second space containing dead air. It is obvious that if the inner and outer copper walls of the calorimeter have the same temperature there will be no exchange of heat between them. Therefore, to prevent a gain or loss of heat by the inner wall, it is necessary to maintain the outer wall always at exactly the same temperature

as the inner wall, under which circumstances the latter cannot gain or lose heat to its neighbor.

"In order to detect differences in temperature between the outer and inner walls Rosa arranged thermo-couples in series between the two walls. In this fashion the top, sides and bottom of the box are successively tested every four minutes by an operator at the observer's table to determine whether there is any difference in temperature between the outer and inner walls. If the outer wall is found to have a different temperature from the inner wall, its temperature is brought to that of the inner wall by the following device. A cooling current of water runs through pipes between the insulating and outer copper wall, and in this same space, along the line of the pipes, run 'Therlo' resistance wires carrying an electric current for the warming of this interspace. By varying the intensity of the electric currents which severally supply the spaces to top, sides and bottom, the temperature of these spaces can be so controlled as to heat or cool the outer copper wall and maintain it at exactly the same temperature as the inner copper wall. This is the effective system which prevents a loss or gain of heat through the wall of the calorimeter.

"Resistance thermometers are attached to the inner walls of the calorimeter, and if the temperature of the walls rises or falls between the beginning and end of the experiment, a correction must be made. It has been found that 19 calories are absorbed by the Sage calorimeter when the inner wall rises 1 degree. Conversely, 19 calories are given up by a fall of 1 degree. This is the *hydrothermal equivalent* of the box.

"The temperature of the air entering the box from the absorbing table is always heated to exactly the same temperature as the air leaving the box.

"Finally, an electric resistance thermometer inserted 10 or 12 cm. into the rectum of the person in the calorimeter gives information regarding the retention or loss of heat in his organism. The specific heat of a man is assumed to be 0.83, that is to say, 0.83 calory raises 1 kilogram 1 degree. If, therefore, the body temperature of a man weighing 70 kilograms rises or falls 1 degree, the quantity of heat lost or gained by the body will be 70×0.83 or 58.1 calories. This is on the assumption that the rise of body temperature is everywhere the same as takes place in the rectum, a supposition which, unfortunately, is not always true.

"The accompanying scheme (Table 13) gives the details regarding the employment of the three individuals who conduct a calorimeter experiment."

TABLE 13.—SCHEME OF EMPLOYMENT OF OBSERVERS IN A CALORIMETER EXPERIMENT.

Period of observation.	Observer 1, at electrical control table.	Observer 2, in charge of experiment.	Observer 3, calculator.
Eight minutes before	Brings wall into exact thermal equilibrium	Signals subject to lie absolutely quiet	Starts passing first 10 L. sample of residual air through U tubes.
Five minutes before	Starts the kymograph record of movements of spirometer.	
Four minutes before	Finishes first and starts second residual.
One-half minute before	Takes final readings of air, wall and rectal temperature	Sets barometer	Finishes second residual.
At "time"	Presses button which diverts stream of water from weighing tank	Shuts the spirometer off from box; fills to the standard level from oxygen tank	Stops ventilating current of air; turns valve to pass air through the newly weighed absorbers; starts the ventilating current.
Immediately after "time"	Starts taking readings every four minutes of ingoing and outgoing water, of air, walls, rectal and surface thermometers; reads and adjusts temperature of top, sides and bottom of calorimeter, of the ingoing air and water every four minutes, or oftener if necessary	Records and sets work-adder; signals to subject that he may move; weighs oxygen tank and connects with box again; weighs sulphuric and soda-lime bottles; connects them up again and tests for leaks; during remainder of hour counts the pulse, inspects valves for leaks, adjusts temperature of the room, watches subject, etc.	Weights the water tank which has received all the water from the heat absorber during the past hour; diverts stream of water to this tank again; records barometer; weighs residual; calculates the results of the hour just finished.

The original Atwater-Rosa-Benedict respiration calorimeter in Middletown was large enough to contain a bed and a bicycle for work experiments and some of the observations lasted many days and nights. Atwater secured a wonderful agreement between the methods of direct and indirect calorimetry with healthy men at rest and at work. The chief disadvantage of his apparatus was its large size which made it necessary to employ a long experimental period and a large staff of observers. Otherwise, it was almost ideal since it gave more information than any other type of apparatus.

The original calorimeter was moved to Washington, D. C., where it is now being used by Langworthy who was actively associated with its early developments. Langworthy and Milner¹ have constructed a smaller calorimeter for the study of plants and small animals which is practically automatic.

¹ Langworthy and Milner: Jour. Agric. Res., 1916, 6, 703.

Benedict's calorimeters in Boston are smaller than the original apparatus and better adapted to short periods. Lusk's calorimeter in New York is just large enough for dogs or babies and is extraordinarily accurate in the measurement of small amounts of heat. The Sage calorimeter in Bellevue is large enough for a patient to lie in bed or sit propped up by a back rest. In this apparatus the experimental periods are usually one hour in length. The total experiment is seldom prolonged beyond three hours as it is difficult to keep patients absolutely quiet for a longer time.

Since the time of Atwater the accuracy of all calorimeters has been tested at frequent intervals by burning within the apparatus a known amount of alcohol. In this manner it is easy to calculate exactly how much heat, carbon dioxide and water should be liberated, how much oxygen consumed. The actual findings are compared with the theoretical figures and the percentage of error becomes apparent. It has been the custom of the Sage staff to publish all the alcohol checks made each year. The series for 1914-1915¹ showed particularly good agreement. The total errors were: heat +0.51 per cent, oxygen -0.51 per cent, carbon dioxide -0.36 per cent, water +3.13 per cent, R. Q. 0.666 instead of the theoretical 0.6666. Errors of 2 per cent in the heat, oxygen and carbon dioxide were frequently found in individual periods of one hour. It is doubtful if the results are any more accurate in experiments on men. On the other hand, the percentage error in the measurement of water is probably not as great, because the burning of alcohol produces so little water that there is a progressive drying of the walls of the calorimeter during the alcohol check.

Benedict Cot Chamber.—The latest and perhaps the best of the respiration chambers which employ only the method of indirect calorimetry is the cot chamber devised by F. G. Benedict.² This is really the same as the Atwater-Rosa-Benedict respiration calorimeter without the elaborate devices which are necessary for the measurement of heat by the direct method. The subject lies on a bed in a small chamber made of galvanized iron. Candor obliges one to admit that

¹ Soderstrom, Meyer and Du Bois: Clin. Cal. 11, Arch. Int. Med., 1916, 17, 872.

² Benedict and Tompkins: Boston Med. and Surg. Jour., 1915, 174, 857; 1916, 174, 898; 1916, 174, 939.

there is some resemblance to a coffin. The cover which is provided with a window is lowered into a trough filled with water which makes an air-tight seal. The apparatus is ventilated by a "Benedict Unit Apparatus" which will be described later. This resembles closely the absorber table of a calorimeter. The carbon dioxide is collected in the soda-lime bottle and weighed. The oxygen consumed is measured by admitting it through a small meter or else by weighing the oxygen cylinder before and after each period. Corrections must be made for the barometer, the temperature of the air in the box, the residual CO_2 and water vapor.

This apparatus is comfortable and accurate, giving good respiratory quotients since there is no tendency to abnormal types of respiration. It has recently been employed with great success by Takahira and by Levine and Wilson.¹ Their alcohol checks are unusually satisfactory. The experiment usually consists of three or more half-hour periods. Continuous experiments of six or eight consecutive hours can be performed. The chief disadvantages are the size, the expense and the length of the experimental period. This machine may not be quite as handy as the portable type for clinical work, but it is certainly well adapted for the problems of a physiological or chemical laboratory.

Short Period Type of Apparatus.—Lavoisier used an apparatus connected with the subject by means of a mask. Regnault and Reiset² in 1849 devised the method of collecting the CO_2 by means of potassium hydroxide and estimating the consumption of oxygen by the shrinkage in volume of the respired air.

The Zuntz-Geppert Apparatus.—This is the machine to which we are indebted for most of our information regarding basal metabolism. The technic is difficult³ but in the hands of trained and careful men extremely accurate. It would not take long to enumerate all the investigators who have shown themselves competent to use this apparatus. It would not be polite to name all who have failed.

The subject is instructed to lie quietly on a couch for at least one-half hour before the experiment and to remain

¹ Levine and Wilson: *Am. Jour. Dis. Child.*, 1926, **31**, 323.

² Regnault and Reiset: *Ann. de chem. et de phys.*, 1849, **26**, 299.

³ Magnus-Levy: *Arch. f. d. ges. Physiol.*, 1894, **55**, 1. Carpenter: *Carnegie Institution of Washington Publication No. 216*, 1915.

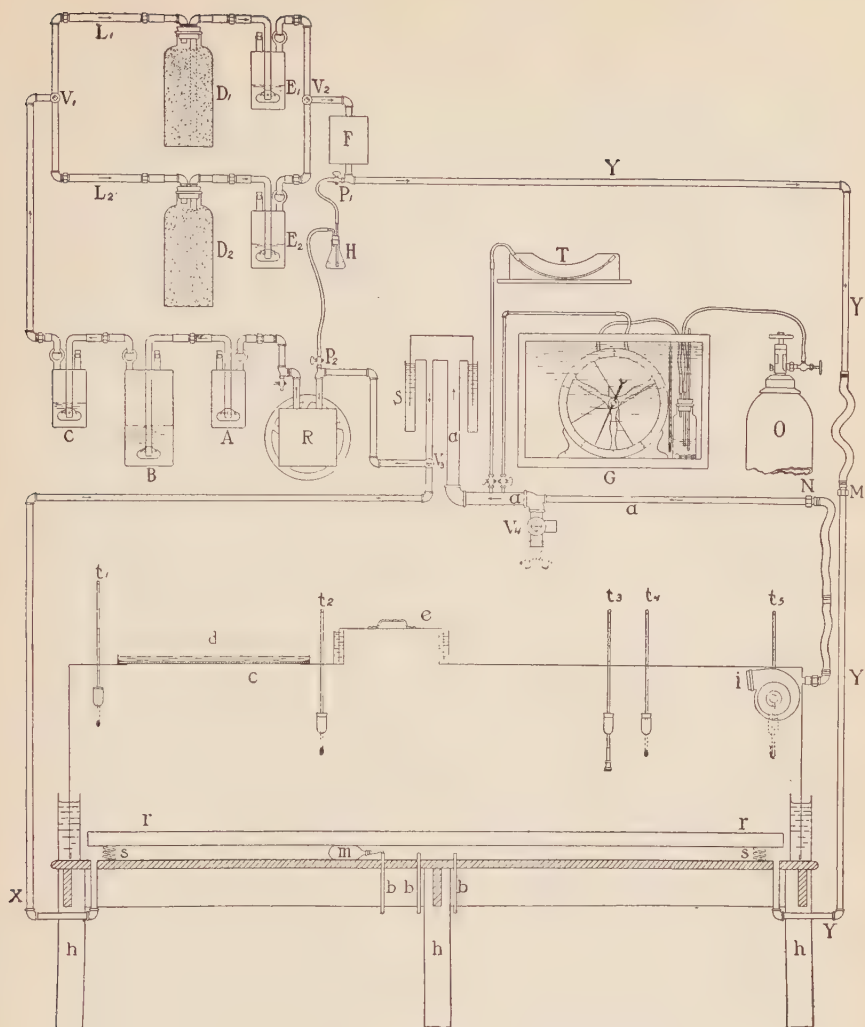


FIG. 10.—Diagram of the Cot Chamber of F. G. Benedict. The upper part of the figure shows the universal respiration apparatus with the following parts: R, blower; A, acid trap; B and C, water absorbers; V_1 and V_2 , two-way valves connecting with the carbon dioxide absorbing system; D_1 and D_2 , carbon-dioxide absorbers; L_1 and L_2 , removable sections of the piping for the introduction of additional carbon-dioxide absorbers; E_1 and E_2 , water absorbers; F, sodium bicarbonate can; P_1 and P_2 and H, pet-cocks and barium hydroxide container for testing the efficiency of the carbon-dioxide absorbers; Y, Y, tube through which the air freed from carbon dioxide and water returns to the chamber; M and N, points at which the tubing is connected when the apparatus is used with a mouth piece or nose pieces; S, spirometer; G, gas meter immersed in water; O, oxygen tank; T, manometer; V_3 and V_4 , three-way valves; a, a, tube connecting chamber with spirometer and oxygen supply. The lower part of the figure shows the respiration chamber. X, outcoming air pipe; i, blower; c, window with water-seal d; e, hand-hole; t_3 and t_4 , psychrometer thermometers; t_1 , t_2 , t_3 , t_4 , t_5 air thermometers; h, h, h, supports for chamber; b, b, b, tubes in bottom of chamber for various connections; r, r, bed; s, s, springs; m, pneumatic bulb.

motionless during the test period. Having had the nostrils closed tightly by a nose clip he breathes through a mouth piece which is connected with a large gas meter of the Elster type. There are valves on either side of the mouth piece so that during inspiration the air is drawn in from the room or from a pipe which connects with the outdoor air. During expiration it is forced through the meter. This measures the expired air and at the same time collects continuous samples in burettes in a water-bath. After ten or fifteen minutes the experiment is ended and the samples of expired air analyzed for CO_2 in caustic potash and for O_2 in a pipette filled with stick yellow phosphorus. Precautions are taken to prevent errors due to change in the temperature or pressure. The calculation is not difficult. Knowing the length of the experimental period, the volume of expired air, the increase in the percentage of CO_2 and the diminution in the percentage of O_2 it is possible to calculate the CO_2 production and O_2 consumption per minute.

The Zuntz-Geppert apparatus is not portable, it is bulky and expensive and the tyro is continually running over solutions into the wrong burettes. Having served its purpose it will probably give way to the Tissot and Benedict types of apparatus.

Tissot Apparatus.—Instead of measuring the expired air in an Elster meter Tissot^{1,2} collects it in a spirometer of most ingenious design. The bell is counterbalanced by a tube of water connected with a syphon so that the counterpoise becomes heavier and heavier as the bell rises. In this manner there is exact equilibrium at all stages of the experiment. This is important since the spirometers employed are large, some containing as much as 200 liters of air though the form most commonly employed contains only 100 liters. Furusawa³ in A. V. Hill's laboratory uses a 700 liter spirometer containing an electric fan in his work experiments, withdrawing samples for analysis at frequent intervals.

Tissot employed glass nose pieces which fitted snugly into the nostrils, the mouth being kept closed. The Thiry valves to separate inspired from expired air were made of thin leaves of brass hinged at the top. The subject after a preliminary rest period inserted the nose pieces, inspired the atmosphere or

¹ Tissot: Jour. de physiol. et de pathol. gén., 1904, 6, 688.

² Carpenter: Carnegie Institution of Washington Publication 216, 1915.

³ Furusawa: Proc. of Roy. Soc. B., 1926, 99, 148.

room air and expired through a long tube connected with a three-way cock. At the start of the actual experiment the cock was turned so that the expired air was diverted to the spirometer. At the end of ten or fifteen minutes the cock was turned to divert the air from the spirometer and the volume of collected air read on a calibrated scale. Corrections were then made for the temperature and barometric pressure and a sample of air withdrawn for analysis of CO_2 and O_2 . Tissot used a rather complicated gas analysis apparatus, but any standard form can be employed.

In this apparatus, as in all others of its type, it is not quite accurate to assume that the volume of the inspired air is the same as the expired. Oxygen is removed and a smaller volume of carbon dioxide is added unless the respiratory quotient happens to be over 1. The nitrogen, however, remains constant and if we know the volume of nitrogen in the expired air we can calculate its total volume.¹ If outdoor air be lead up to the intake valve by means of a large pipe we can be certain of its composition without analysis. Knowing the CO_2 and O_2 of the expired air we can easily calculate the subject's metabolism.

The Tissot apparatus is accurate and lends itself well to many experiments on the physiology of respiration. It is somewhat expensive and bulky and the technic of air analysis is rather difficult requiring at least a solid month of practice. Most investigators in this country consider it the best machine for research work in the clinic. If the technician is not accurate it becomes evident at once that something is wrong with the results. The accuracy of the air analysis is easily checked by routine examinations of the outdoor air. The machine is not fool-proof, but it is a fool-detector.

In this country there have been several modifications of the original technic. Some use an eccentric wheel to balance the spirometer bell at all levels. Few still employ the nose pieces. Mouth pieces or carefully fitted masks are better. Instead of the Thiry flap valves, numerous other devices are

¹ In order to find the true volume of oxygen in the incoming air corresponding to 100 volumes of outgoing air the following formula should be employed: The percentage of nitrogen in the incoming air is to the percentage of nitrogen in the outgoing air as the percentage of oxygen in the incoming air is to the volumes of oxygen in the incoming air. See Table II, p. 103. Carpenter: *Tables, Factors and Formulas for Computing Respiratory Exchange and Biological Transformations of Energy*, Pub. No. 303. Carnegie Institution of Washington, 1921. Also table on p. 62, Haldane, *Methods of Air Analysis*, London, Griffin & Co., 1918,

employed, gas-mask flap valves or the Soderstrom model of the Lovén diaphragm valve.¹ Boothby and Sandiford² who have made thousands of tests with this apparatus in the Mayo Clinic have described their technic in great detail. Bailey³ has added practical improvements.

*The Douglas Bag.*⁴—This device is light and can easily be carried on a subject's back. Instead of a meter or spirometer the air is collected in a wedge-shaped rubber bag which will hold from 30 to 100 liters. The mouth piece is supported by a head harness and a large bore three-way valve diverts the expired air to the bag when the experiment is started. On either side of the mouth piece are Douglas valves which consist of thin circular pieces of mica resting on the smooth ends of brass tubes. These should be kept upright so that gravity helps to seat the mica flaps.

At the end of an experimental period the volume of the expired air is measured in a meter and a sample removed for analysis.

This apparatus is well adapted for walking experiments and it is used in England for determinations of the basal metabolism in short periods. A. V. Hill⁵ employs a battery of these bags, switching from one to the other in order to collect continuous samples over a long period. He has studied carefully the very considerable errors in the measurement of carbon dioxide and oxygen when the subject begins to breathe mixtures containing high percentages of oxygen.

Benedict Universal Respiration Apparatus (Unit Apparatus).—This is a closed circuit apparatus in which Benedict⁶ uses the principles applied by him to the Atwater-Rosa calorimeter. Instead of a large chamber enclosing the whole subject, the respiratory tract alone is connected with the system of pipes and absorbing bottles. By means of a mouth piece or tight nose pieces the man is attached to the respiration apparatus and he uses the same air over and over again. The water is removed by sulphuric acid, the carbon dioxide by soda-lime. As the oxygen is consumed it is replaced from a cylinder so that the air remains pure and respirable. A

¹ McCann: Arch. Int. Med., 1921, 28, 847.

² Boothby and Sandiford: Laboratory Manual of the Technic of Basal Metabolic Rate Determinations, Philadelphia, W. B. Saunders Company, 1920.

³ Bailey, C. V.: Jour. Lab. and Clin. Med., 1921, 6, 657.

⁴ Douglas: Jour. Physiol., 1911, vol. 42, xvii.

⁵ Hill, A. V.: Proc. Roy. Soc., 1924, 97, 84.

⁶ Benedict: Am. Jour. Physiol., 1909, 24, 345; Deutsch. Arch. f. klin. Med., 1912, 107, 156.

rubber tension equalizer or well-balanced spirometer allows for the change in volume during inspiration and expiration and shows the shrinkage in volume which calls for the admission of more oxygen. The absorber table with its pipes and bottles is a small model of the one used in connection with the calorimeter.

The subject breathes through a mouth piece or nose pieces and a large three-way valve which can be turned to connect either with the room air or with the tubing of the apparatus. A current of air is continually propelled through this tubing by means of an electrically driven blower at a rate which assures a plentiful supply of purified air during inspiration. The expansion caused by expiration is taken care of by the spirometer close to the mouth piece. The air is drawn through this spirometer to the blower and then forced through Williams' bottles containing strong sulphuric acid to remove all moisture. Thence it is driven through a detachable soda-lime bottle which removes all the CO_2 and a sulphuric acid bottle which catches all the moisture from the soda-lime. The combined increase in weight of these two bottles gives the carbon dioxide production. Leaving these it is driven through water or sodium bicarbonate solution to catch the faint acid fumes and once more passes the three-way valve attached to the mouth piece. The oxygen can be admitted at any point in the circuit either from a weighed cylinder or through a small Bohr meter.

Before the experiment begins the patient lies quietly on a couch for at least one-half hour to exclude the effect of previous muscular activity. Meanwhile the operator has weighed the soda-lime and sulphuric bottles and the oxygen cylinder, has connected them securely with the system of pipes and has tested carefully for leaks by running the apparatus for several minutes and proving that the spirometer remains at exactly the same level. Next the mouth piece or nose pieces are attached and the patient allowed to breathe through the three-way valve which has been turned so as to connect with the room air. When the observer is convinced that the respiration is regular he waits until the end of an expiration and turns the valve so as to connect the lungs with the apparatus. At the same instant he starts his stop-watch. The spirometer now begins to rise and fall regularly with the respiration and a record is made by means of a pointer which writes on the smoked paper of the kymograph. The oxygen

in the circuit is gradually consumed and the spirometer falls a little further at the end of each respiration making as a rule a perfectly regular curve. After the spirometer has fallen a few inches it is raised to about its previous level by admitting oxygen from the cylinder. At the end of ten or fifteen minutes the observer again watches for the end of an expiration and turns the valve so that the subject no longer breathes into the apparatus. He then allows the blower to run for a few minutes longer to sweep out all the traces of CO_2 and then carefully admits oxygen until the pointer on the spirometer has come to the same level as at the start of the experiment. It is obvious that the cylinder has lost exactly as much oxygen as the subject has consumed.

Benedict has made many improvements since his first 1908 model. At this time he used a rubber bathing cap instead of a spirometer and Woulfe bottles for the sulphuric acid. It was found that the oxygen cylinders often developed leaks in the reducing valves making weighings inaccurate, so he adopted the method of measuring this gas in a small Bohr meter immersed in a water-bath. This, of course, must be watched carefully each time oxygen is admitted and a record made of the exact amount.

This Benedict Universal Apparatus made most of the determinations on which we now base our statistics of the basal metabolism. It is a perfectly good machine if you know how to run it, but it can develop leaks at a surprising rate. The writer had occasion to test out one of the first of these machines made outside of Benedict's laboratory. In the first few days about a dozen leaks were discovered in various joints and tubes. Then there remained one obscure leak that could not be located for a week. The machine was transported to the hospital across the street and an entirely new crop of leaks appeared. Unless the rubber gaskets are just right there will be leaks when the joints are made up after weighing the soda-lime and sulphuric bottles.

The original nose pieces often began to leak in the middle of an experiment. Mouth pieces, now more commonly employed, give less trouble. Of course, every leak of 100 cc causes just this much error in the oxygen reading. Constant vigilance, frequent testing and much patience are necessary.

As far as the subject of the experiment is concerned, this type of apparatus is fairly comfortable. There is a slight odor to the air, a slight resistance to respiration and slight dis-

comfort from the nose pieces or mouth piece. On the other hand, the hum of the motor and faint throbbing of the air tend to produce a drowsiness. Some patients fall asleep, others develop an uncontrollable tendency to "auspumpung" and breathe so deeply that they wash the loosely stored carbon dioxide from their blood and tissues.

At the present time this machine is not much used. The large but accurate balances needed for the weighings are expensive and difficult to obtain. Benedict's "Portable" apparatus has displaced the "Universal."

Modification of Rolly and Rosiewitz.—Rolly and Rosiewitz¹ have made a few modifications of the Benedict Universal apparatus but have materially added to the complexity without much apparent improvement in accuracy.

*Benedict Portable Apparatus.*²—This is a logical development of the "universal" or "unit" apparatus made very compact so that it can be moved about a hospital. It is intended primarily for the measurement of oxygen consumption. If we assume that the respiratory quotient will be 0.82 in the morning at least fourteen hours after the last meal, we can employ the calorific value of a liter of oxygen 4.825 which will be sufficiently accurate for clinical purposes. This does not take into account the fact that we derive about 15 per cent of our calories from protein, and if we make the necessary allowance for this a factor of 4.78 would be obtained for a respiratory quotient of 0.82. In basal experiments in the calorimeter the quotient is usually between 0.80 and 0.84 but may be as low as 0.78 or as high as 0.90. The proper factor for the calorific value of oxygen may be anywhere between 4.7 and 4.9.

The main part of the Benedict Portable apparatus is the long spirometer with a carefully calibrated scale on the side. The oxygen consumption is measured by the fall of this spirometer. The CO₂ is removed from the circulating current of air by a soda-lime bottle. If the operator wishes to weigh the CO₂ he uses sulphuric acid or calcium chloride granules before and after the soda-lime but these are usually omitted. The air is kept in circulation by a small blower of the type used in drying hair. The whole affair is mounted on a small stand and the tubes leading to the three-way valve and mouth piece are carried on an adjustable arm.

¹ Rolly and Rosiewitz: *Deutsch. Arch. f. klin. Med.*, 1911, 103, 58.

² Benedict: *Boston Med. and Surg. Jour.*, 1918, 278, 667.

The technic of the experiment differs slightly from that of the "unit" apparatus. Before the observation begins the spirometer is filled with oxygen. The subject, therefore, breathes a mixture much richer in oxygen than the ordinary

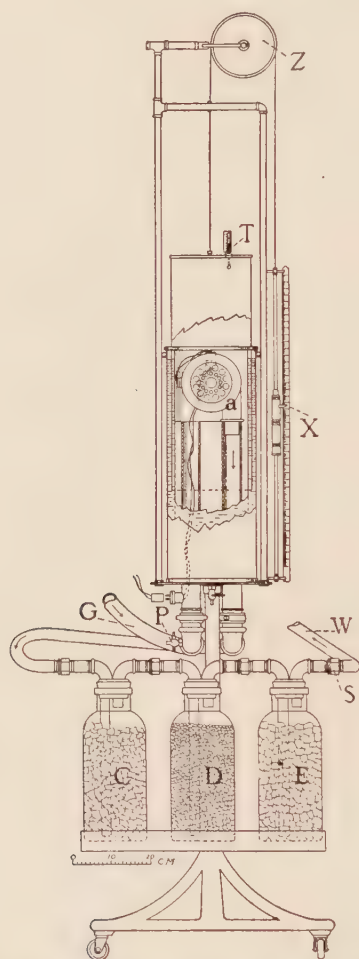


FIG. 11.—Spirometer and absorbing system of portable respiration apparatus *G*, large caliber pipe conducting expired air to spirometer; *a*, air impeller; *C* first water absorber; *D*, carbon-dioxide absorber; *E*, second water absorber; *S*, point at which rate of ventilation may be tested by disconnecting coupling; *W*, pipe conducting purified air to subject; *P*, pet-cock for introduction of oxygen; *T*, thermometer for obtaining records of temperature of spirometer. The spirometer bell is counterpoised by the weight, *X*, attached to silk thread passing over aluminum wheel, *Z*. Scale on which pointer indicates height of spirometer bell is shown beside *X*. (Benedict.)

air, but this causes no change in the metabolism and no error after the first few breaths have established the new equilibrium in the lungs.

The subject breathes through a mouth piece but instead of starting the experimental period when he is first connected with the closed circuit the operator waits a few minutes until the respiration is perfectly regular. Then he notes the reading at the end of an expiration and starts the stop-watch. He records this and the corresponding readings at the end of three, six and twelve minutes. After a few minutes he places a weight on the spirometer to increase the pressure and notes if the spirometer falls more rapidly than before. This will detect even a small leak in the apparatus. After a sufficient number of readings the experiment is ended. Corrections are made for the temperature, barometer and moisture in the spirometer and the liters oxygen consumed are multiplied by the calorific value of oxygen for a respiratory quotient of 0.82. The use of this apparatus is further explained in articles by Benedict¹ and Roth.² Its accuracy has been checked by Hendry, Carpenter and Emmes.³ The Sanborn Company of Boston has put on the market a modification called the Benedict-Sanborn. Benedict and Collins⁴ have made several improvements on the original portable. In some of these portables the electric blower is inside the spirometer. This is sometimes a source of trouble. It requires but a small spark to start a fire in the oxygen-rich mixture. Such accidents, of course, are much more frequent in the hands of beginners, and they practically never occur in a laboratory like Dr. Benedict's. Nevertheless they constitute a serious drawback, as such a fire is alarming through not particularly dangerous. In some of the machines the electrical part of the blower is outside the apparatus obviating the danger of fire but providing another place for possible leakage.

The Metabolor.—The Toledo Technical Appliance Company has devised an apparatus called the McKesson Metabolor which is built on the principle of the wedged-shaped Krogh spirometer. This is an attractive looking apparatus, but I

¹ Benedict: Boston Med. and Surg. Jour., 1920, 182, 243.

² Roth: Boston Med. and Surg. Jour., 1921, 184, 222.

³ Hendry, Carpenter and Emmes: Boston Med. and Surg. Jour., 1919, 181, 285., 334, 368

⁴ Benedict and Collins: Boston Med. and Surg. Jour., 1920, 183, 449.

have had no personal experience in its operation. Hannon and Lyman¹ using a graphic recorder obtained excellent agreement with the Tissot apparatus. An improved graphic attachment is now incorporated in the machine.

The Jones Metabolimeter.—Jones² of Chicago has devised an extremely ingenious apparatus shown in Fig. 12. This consists of a device for measuring a liter of oxygen, an absorbent for CO₂ and rubber bag to expand and contract with respiration. The observer measures the average time required to consume a liter of oxygen. Opinions seem to differ as to the accuracy of the apparatus, but many observers have obtained satisfactory results.

The Sanborn Handy Model.—The Sanborn Company has placed on the market a small spirometer without a blower. In the original model there was a long breathing tube with a large dead space. This has recently been changed and valves substituted. A graphic attachment was added but in 1926 the spirometer was still without a counterbalance. Hunt³ in a series of 25 cases found that the Handy model gave results distinctly higher than those obtained with the Douglas bag but concluded that the former was accurate within + or - 12 per cent in 80 per cent of the cases. Particular care must be used in any apparatus where the spirometer is not accurately counterpoised since air pressure increases the tendency toward leakage.

The Benedict-Roth Apparatus.—Dr. Paul Roth⁴ has devised a simplification which seems to be extremely satisfactory. He has removed the electric blower and has substituted rubber "flutter valves" of the type devised by Major Sadd for gas masks. The extra resistance seems to be negligible, as it requires very little respiratory effort to drive the air through the valves, tubing and soda-lime. After the patient has been connected with the apparatus and has breathed into it for one or two minutes, several readings are taken at the end of expirations, the time of each being noted exactly. Other readings are taken exactly six minutes after each of the original readings. Corrections are made for temperature, barometric pressure and moisture. Roth has improved the

¹ Hannon and Lyman: Johns Hopkins Hosp. Bull., 1923, 34, 241.

² Jones: Jour. Am. Med. Assn., 1920, 75, 538; Arch. Int. Med., 1921, 27, 48.

³ Hunt: Lancet, 1926, i, 172.

⁴ Roth: Boston Med. and Surg. Jour., 1922, 186, 457, 491; Bull. Battle Creek San., 1923, 18, 131.

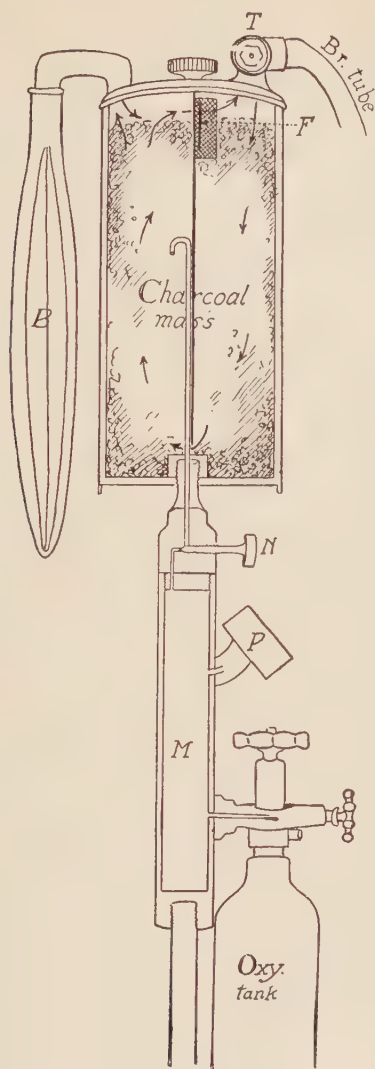


FIG. 12.—Cross-section of apparatus: Arrows indicate direction of movement of inspired and expired air; *Br. tube*, breathing tube; *T*, three-way cock; *F*, flutter valve for directing circulation of gases; *B*, rubber bag to contain measured amount of gas and to allow for expansions and contractions in respiration; *N*, needle valve for releasing the measured amount of oxygen from *M*, the measuring cylinder, into the charcoal-alkali tower above; *P*, pressure gauge with room-temperature scale on dial to indicate when 1 liter of dry oxygen at 0° C. and 760 mm. has been released at any given room temperature from the oxygen tank. (Jones.)

technic by attaching a kymograph. When a tracing of the respiration is made with the record of an accurate time marker on the same paper it is possible to obtain a much more exact determination of the rate of oxygen consumption. A portion of the curve covering three, six or more minutes of regular respiration is selected and a line drawn connecting the points which represent the end of expiration. The number of millimeters fall per minute or hour can thus be measured and translated into calories after making the proper calculations according to the diameter of the spirometer, the temperature, barometric pressure etc. The recording device was suggested by Dr. F. G. Benedict many years ago in connection with his universal respiration apparatus. Coleman and the writer on Dr. Benedict's¹ suggestion used a graphic record in 1912 in their studies on typhoid fever and found it of great service.

Wilson² has published a note on the humidity of air in the apparatus when his soda-lime is used. Roth has expanded Wilson's formula into a table which aids in making the correction for water vapor. Simple and inexpensive looking modifications have been described by Herxheimer³ and Schadow.⁴

*The Krogh Apparatus.*⁵—Professor August Krogh⁶ of Copenhagen who has devised many different types of respiration apparatus for research work, has recently made a simple model which seems to be admirably suited to clinical purposes (Fig. 13). He also uses a recording device. This was developed independently of the American types of apparatus. Krogh and Rasmussen⁷ found that it was just as accurate as the type of apparatus which measured and analyzed the expired air over a similar period, but showed a tendency to give results 1 to 2 per cent lower.

The Benedict Student Apparatus.—Francis G. Benedict and Cornelia Golay Benedict⁸ have simplified the Benedict

¹ Benedict: *Deutsch. Arch. f. klin. Med.*, 1912, 107, 156.

² Wilson: *Boston Med. and Surg. Jour.*, 1922, 187, 133.

³ Herxheimer: *Deutsch. med. Wchnschr.*, 1925, 51, 1143.

⁴ Schadow: *Klin. Wchnschr.*, 1925, 4, 1548.

⁵ The details of apparatus and technic have been described in a circular issued by H. N. Elmer, 1641 Monadnock Bldg., Chicago.

⁶ Krogh: *Wien. klin. Wchnschr.*, 1922, 35, 290; *Boston Med. and Surg. Jour.*, 1923, 189, 313.

⁷ Krogh, M., and Rasmussen: *Wien. klin. Wchnschr.*, 1922, 35, 803.

⁸ Benedict and Benedict: *Boston Med. and Surg. Jour.*, 1923, 188, 567.

portable apparatus to such an extent that it can be manufactured for an exceedingly small cost. Instead of a metal spirometer they use a rubber bathing cap which can be filled until it exactly touches a given mark. As the patient consumes oxygen, air is introduced by means of a calibrated pump and the number of strokes of this pump for a given time shows the volume of oxygen removed from the apparatus. Although the Benedicts recommend this chiefly as a model for student use, there are indications that it will prove sufficiently accurate for clinical purposes (Fig. 14).

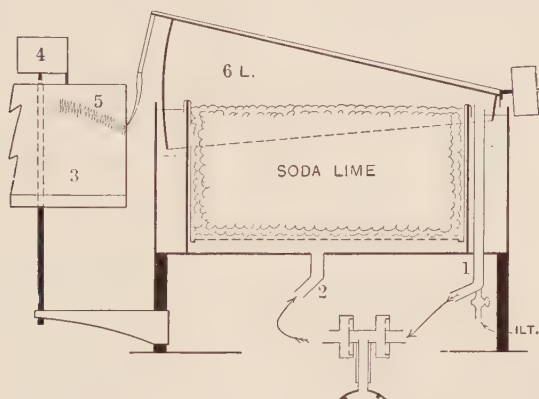


FIG. 13.

Apparatus for Measuring Carbon Dioxide as well as Oxygen.—It is highly desirable to determine the carbon dioxide excretion at the same time as the oxygen consumption if this can be accomplished without too great an expenditure of time. Several extremely ingenious types of apparatus have recently been described by Hagedorn,¹ Knipping,² Helmreich and Wagner,³ Dusser de Barenne and Burger,⁴ and Dethloff⁵ but as yet they have not been extensively employed and tested. All of these machines dispense with air analyses and weighings and record the CO₂ graphically.

¹ Hagedorn: *Biochem. Jour.*, 1924, 18, 1301.

² Knipping: *Münch. med. Wchnschr.*, 1924, 71, 553; 1925, 72, 2095; *Deutsch. Arch. f. klin. Med.*, 1924, 145, 179.

³ Helmreich and Wagner: *Klin. Wchnschr.*, 1924, 3, 406; *Biochem. Ztschr.*, 1924, 149, 560.

⁴ Dusser de Barenne and Burger: *Klin. Wchnschr.*, 1925, 4, 68.

⁵ Dethloff: *Klin. Wchnschr.*, 1925, 4, 2441.

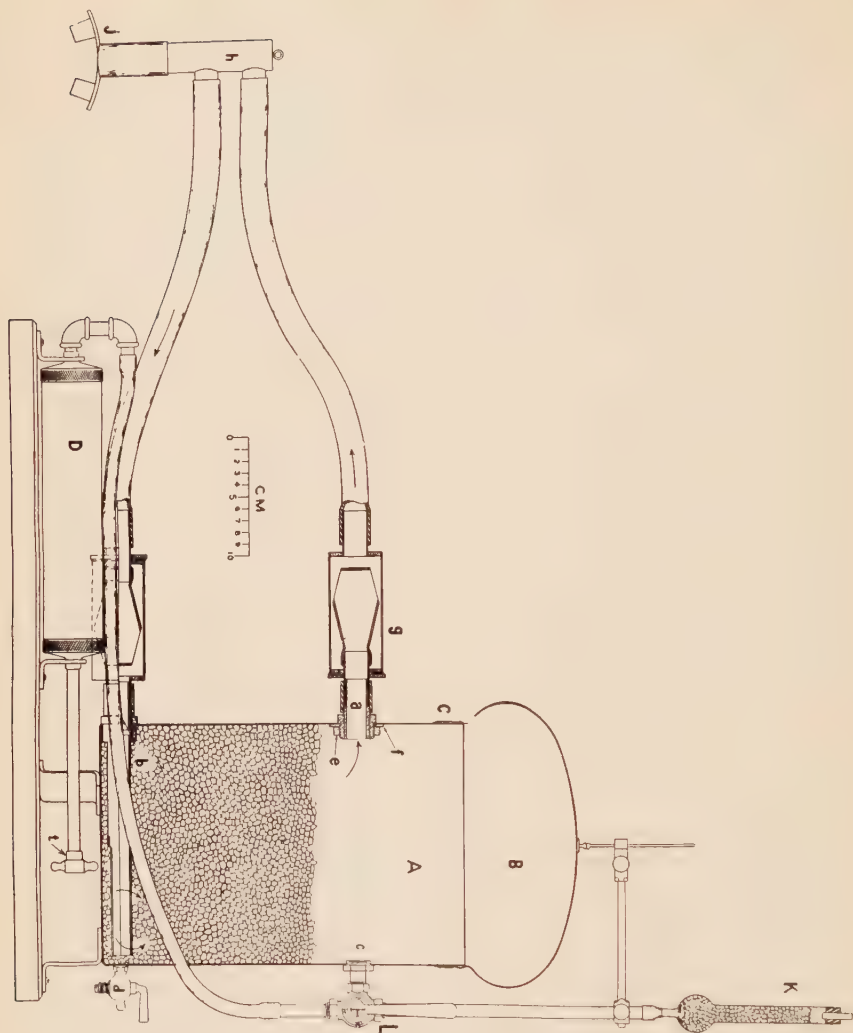


FIG. 14.—A student form of respiration apparatus. *A*, metal can partly filled with soda-lime; *B*, rubber bathing cap, held in place by rubber band, *C*. The subject breathes through the mouth piece, *j*, which is attached to the metallic piece, *h*, connecting with two rubber tubes leading to Sadd respiratory valves on the can, *A*. The expired air enters through the opening, *b*, and is returned to the subject, freed of carbon dioxide through the opening, *a*. The Sadd valves are enclosed in light brass housings, *g*. The opening, *a*, is stiffened by a lock nut, *e*, and a small, flat piece of iron, *f*, curved to fit the can. Oxygen for preliminary enrichment is admitted through the pet-cock, *d*, and measured amounts of dry air, drawn through the calcium chloride tube, *K*, into the pump, *D*, are forced into the can through the valve, *L*, and the opening, *c*, (Benedict.)

*The Hagedorn Apparatus.*¹—Hagedorn's machine is of the closed circuit type, the air being circulated by two symmetrical gas meters arranged on a common shaft, revolved by a small electric motor. Each gas meter is attached to a spirometer of the Krogh type, and the movements of both spirometers are recorded on a revolving drum. Gas meters and spirometers are all immersed in a common water-bath, thus securing equal temperatures. The patient breathes through the ordinary type of mouth-piece attached to a pipe leading to the first gas meter. Thence the air passes to spirometer *A* in the bottom of which is a layer of moist soda-lime to absorb CO_2 . The second gas meter withdraws from the top of the spirometer *A* exactly the same amount of air as was driven into it by the first gas meter. Therefore the fall in level of spirometer *A* measures the volume of CO_2 absorbed. The air from the second gas meter is then delivered into spirometer *B* whence it passes directly to the tube on the side of which the mouth-piece is attached, thus completing the closed circuit. Air is delivered into spirometer *B* by the second gas meter and exactly the same amount is withdrawn by the first gas meter, but since the patient breathes into the tube, the volume change in the air represents the volume of oxygen absorbed minus the volume of CO_2 produced. Since spirometer *A* has recorded the CO_2 , it is easy to find the oxygen consumption.

The technic does not look easy and it is necessary to run blank tests in order to make the necessary corrections for the slight unavoidable differences in the capacities of the two revolving drums. Dr. D. P. Barr of Washington University, St. Louis, has given enthusiastic verbal reports regarding this apparatus.

Alcohol Checks with Portable Respiration Apparatus.—We have already spoken of the method of testing the accuracy of the respiration calorimeter by burning a known amount of alcohol and comparing the gases actually measured with the quantities theoretically produced or consumed. Carpenter and Fox² have devised an apparatus which permits such a test with portable respiration machines and Benedict³ has made certain improvements which are shown in Fig. 15.

¹ Hagedorn: *Biochem. Jour.*, 1924, **18**, 1301.

² Carpenter and Fox: *Boston Med. and Surg. Jour.*, 1923, **189**, 551.

³ Benedict, F. G.: *Ibid.*, 1925, **193**, 583.

A strong solution of alcohol of known percentage is burned in a glass combustion chamber which connects with the tubing of the respiration machine. An automobile windshield wiper supplies the motive power which actuates a spirometer (artificial lung) and also lowers a burette so that the alcohol flows to the lamp at a constant rate. This device is simple and I trust that every investigator will test his apparatus in some such manner.

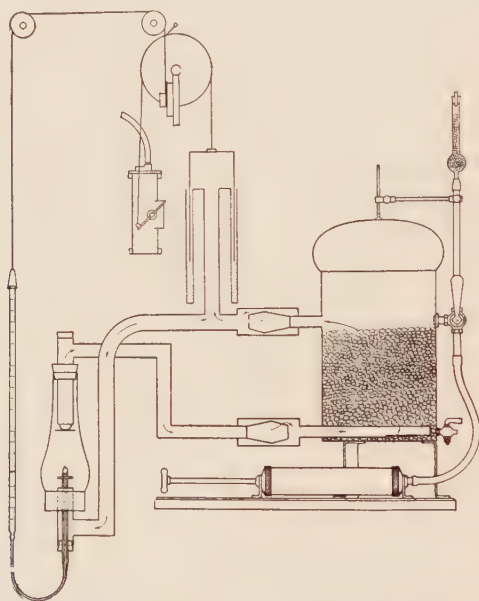


FIG. 15.—Mechanico-chemical device connected with student respiration apparatus. (Benedict.)

APPARATUS FOR THE STUDY OF THE RESPIRATORY METABOLISM OF CHILDREN.

Practically all the instruments used for children are small models of the chambers described above. An excellent description of methods and findings has recently been given by Murlin.¹

There are few things more difficult than the determination of the basal metabolism of children. Infants are never quiet

¹ Murlin: *Abt's Pediatrics*, Philadelphia, W. B. Saunders Company, 1923, I, 520.

except when asleep. They do not sleep well unless they have food in the stomach. This causes a rise above the basal level which is usually disregarded. When quiet they give off so little carbon dioxide and consume so little oxygen that the measurements are difficult. The experimenter can never predict when a quiet period will be terminated by a sudden increase in the moisture, or by a howl of anger. Children from two years to ten years of age are not at all easy to handle. Short periods must be used and mouth pieces, nose pieces or masks seem difficult of application but Helmreich¹ was able to employ the Krogh graphic method with one child a year and three-quarters old.

The early work was done with a Pettenkofer-Voit chamber just large enough to hold a child's cot. Even this was too large and it was impossible to get short periods of purely basal metabolism. The experiments were of value in establishing the caloric output under the ordinary living conditions with a mixture of basal periods and active periods. The Sondén and Tigerstedt apparatus was used for older children who were allowed to sit upright in chairs and eat apples and candy. Magnus-Levy and Falk succeeded in using the Zuntz-Geppert apparatus with mouth pieces for children over two and a half years and apparently obtained fairly good results, though their figures are somewhat higher than those of subsequent observers.

Schlossmann and Murschauser² used for infants a small box immersed in water which maintained a constant temperature. They kept a careful record of the muscular activity and were able to select the basal periods.

Howland³ working with Lusk's dog calorimeter, an ideal instrument for the study of babies, established the fact that the methods of direct and indirect calorimetry show close agreement.

Benedict^{4,5} devised for children a small cot chamber which he surrounded by a water jacket and employed a sensitive device to record graphically every movement of the child. This is one of the most satisfactory instruments for general

¹ Helmreich: *Klin. Wchnschr.*, 1925, 4, 540.

² Schlossmann and Murschauser: *Biochem. Ztschr.*, 1910, 26, 14.

³ Howland: *Ztschr. f. physiol. Chem.*, 1911, 74, 1.

⁴ Benedict and Homans: *Jour. Med. Res.*, 1912, 25, 409.

⁵ Benedict and Talbot: *Am. Jour. Dis. Child.*, 1912, 4, 129; Carnegie Institution of Washington Publication No. 201, 1914.

use, since it is much simpler than the respiration calorimeter. This cot chamber was used by Talbot and by Levine and Wilson¹ with great success. Murlin² developed a respiration apparatus for babies, placing a small box in a Freas electric incubator which automatically maintained a constant temperature. This machine has proved to be very accurate and useful.

The Selection of a Respiration Apparatus.—The most accurate of all the instruments is the respiration calorimeter of the Atwater-Rosa-Benedict type since it measures the metabolism by two independent methods. The Benedict Cot Chamber can probably be just as accurate. The smaller machines with mouth pieces, etc., do not measure the carbon dioxide excreted through the skin, but the general opinion is that this does not amount to 1 per cent of the total excretion. We have no figures on the possible absorption of oxygen through the integument.

In the hands of experienced technicians there is practically no difference in results obtained with the Benedict Unit, Zuntz-Geppert, Tissot Spirometer and Douglas Bag, and all agree with the respiration calorimeter. The Benedict Portable and Benedict-Collins measure the oxygen consumption accurately; but may show an error of 1 or 2 per cent on account of the assumption that the respiratory quotient is 0.82. As a matter of fact, it is doubtful if we can ever be sure that any respiration test is accurate within 2 per cent, unless we make repeated observations on several days. This error may be exceeded by the variation in the metabolism of the individual himself from day to day, or even from hour to hour.

The selection of the proper type of respiration apparatus depends entirely upon the problems to be solved. For the ordinary hospital the most suitable outfit at the present time seems to be some type of closed circuit apparatus with a small well balanced spirometer and a graphic attachment. For ordinary clinical work we can dispense with the carbon dioxide, and it does not seem necessary to have an electric blower in the circuit. As a matter of fact most of the errors lie not in the machines but rather in those who operate them.

In the hospital used for teaching and research work there is a much better financial support for the laboratory and a

¹ Levine and Wilson: *Am. Jour. Dis. Child.*, 1926, 31, 323.

² Murlin: *Am. Jour. Dis. Child.*, 1915, 9, 43.

larger staff of trained chemists. For such an institution the Tissot spirometer is highly recommended. The ideal valve for this has not yet been invented, but at the present time the favorite types are the gas mask flutter valve, the Thirty-Tissot brass flap valves and the Soderstrom model of the Lovén valve. Mouth pieces are less liable to leak than masks or nose pieces. Masks are comfortable for the patients and can be made air tight by experienced operators. The standard apparatus for air analysis is the Haldane Portable but the Henderson apparatus with the slight modifications made in the Sage laboratories is just as accurate and much simpler.

The best apparatus for teaching the physiology of nutrition is the Benedict Universal. Students can make accurate weighings but seldom make a good enough analysis of the expired air to use the Tissot spirometer. They should certainly study the carbon dioxide excretion and the respiratory quotient and not be content with the fragmentary data furnished by the so-called "Portables."

The Benedict Universal is a particularly useful apparatus in any laboratory engaged in research problems. It can be attached to the Benedict Cot Chamber or to a small box used for animals or babies.

Respiration calorimeters are recommended only for those who have problems which deal with the regulation of body temperature, radiation, conduction, vaporization, etc., or with the intermediary metabolism.

Management of Basal Tests.—There is a tendency at the present time in some hospitals to turn over the management of the metabolism laboratory to a technician who has had no training in medicine or the science of nutrition. Such people often do well in metabolism work just as in roentgen-ray diagnosis or bacteriology. On the other hand they can scarcely be blamed if they get far off the track and make disastrous errors. They may be excellent in their technic, but the management of experiments and the interpretation of results in patients should be in the hands of a clinician who has made some special study of metabolism. This man should be thoroughly familiar with the technic himself as it is only in this manner that he can be on guard against all the possible errors.

When a laboratory first receives its respiration apparatus there should be a thorough testing for leaks and a recalibra-

tion of burettes, spirometers, etc. If possible the machine should be tested by alcohol checks. Next a series of many normal controls should be studied to see if the results conform to the normal standards. This, however, cannot prove the accuracy of the machine much closer than 5 per cent but it is better than nothing and gives experience in the technic. The duplicates should be examined and the work kept up until they agree within 5 per cent. One or two of the normal controls who are readily available should be studied at frequent intervals throughout the year since they ought to maintain a fairly constant metabolism. If the machine shows a sudden change in the metabolism of one of these test individuals trouble should be suspected. Some clinicians have fallen into the utterly reprehensible habit of thinking that the machine is all right if it makes estimations of thyroid activity which correspond with the clinical diagnosis. "How's your machine, Doctor?" "All right; the results check up clinically." Galen must have used the same phrase when questioned about his *Pharmacopœia*.

Any clinician who sends patients to a laboratory for basal metabolism tests has a perfect right to ask to see the list of normal controls studied on the same apparatus. He should also ask to see the duplicates and if the Tissot type of apparatus is used he should ask to see the recent analyses of outdoor air. If the technician raises the slightest objection to granting any one of these requests, something is wrong somewhere.

Many serious errors can be made in the management of the patient. In the first place one should secure perfect coöperation by explaining that the test is necessary and is for the patient's good. He must be instructed to take no food in the evening after 8 o'clock and nothing in the morning except a cup of caffeine-free coffee without milk or sugar. He must be brought to the laboratory without fatigue, on his arrival weighed and measured to determine his height. He must lie quietly for at least one-half hour before the test.¹ The mouth temperature should be taken and the pulse counted at intervals until it has assumed a basal level. The atmosphere of the room should be quiet and confident and there should be as little display of apparatus as possible. Visitors must be excluded.

¹ Benedict and Crofts: *Am. Jour. Physiol.*, 1925, **74**, 369.

If the subject has not had previous training he must be put through a short "dummy" test to demonstrate the fact that there is no actual discomfort to the procedure. Following this two or three actual measurements of the basal metabolism should be made. It is advisable to keep a record of the respiration and muscular activity but not wise to annoy a nervous subject with too much paraphernalia. Of course, a careful watch must be maintained for leaks around a mouth piece or mask and if there be a graphic attachment a test for leaks made in the middle of the period. This is accomplished by placing a small weight on the spirometer for two minutes and observing any change in the rate of fall.

If the results in the tests do not agree fairly closely another must be undertaken. If the subject is tired or restless an appointment should be made for another morning. In all borderline cases the test must be repeated.

The man who conducts metabolism experiments should be perfectly frank with himself regarding the accuracy of his results. He should estimate the possible percentage of error and never try to conceal from himself the fact that the technic of a certain experiment was rather poor. This seems to be only common honesty but it is rather difficult to practice. Having made an experiment it becomes your own, and you are fond of it. It is only after much bitter experience that you learn to discard all questionable results. They lead you to false conclusions which bring endless trouble. They destroy your self confidence and the confidence of others:

"This above all: to thine own self be true,
And it must follow, as the night the day,
Thou canst not then be false to any man."

CHAPTER VI.

THE ESTIMATION OF THE SURFACE AREA OF THE BODY.

At the present time it is customary in many laboratories to express the results of metabolism tests in terms of calories per square meter of body surface. The reasons for this will be discussed later, but it seems advisable at this point to describe the various methods of determining surface area.

Probably the earliest published work on surface area measurements is that of John Abernethy. This was rediscovered in 1925 by Dr. F. G. Benedict who has kindly brought it to my attention. Abernethy¹ calculated the surface of the cylindrical parts of the body from the length and mean circumference and computed the surface of the head, hands and feet "by applying paper cut as the occasion required, over these parts; afterward placing the separate pieces of paper, so as to form an extended plain" He gives the surface of a man 5 feet 6 inches high as 2700 square inches. Unfortunately he does not state how much the man weighed. According to our latest surface area formula his measurement is absolutely correct if the man weighed 143 pounds.

The first really extensive work on the subject was done by Meeh² in 1879. He measured 6 adults and 10 children, using various methods, such as marking out the body in geometrical patterns, winding strips of millimeter paper around the limbs, cutting out and weighing pieces of paper which covered portions of irregular shapes, etc. On the strength of these 16 individuals, Meeh devised a formula which gave results within 7 per cent of his actual findings. He rather naturally used the two-thirds power of the weight in his formula, since the surface areas of two objects of the same shape are to each other as the two-thirds power of the volumes. Raising a number to the third power makes a cube of it; taking the square root reduces it to two dimensions. Meeh found that,

¹ Abernethy, John: Surg. and Physiol. Essays, Part II, London, 1793, p. 134.

² Meeh: Ztschr. f. Biol., 1879, 15, 425.

if he multiplied the cube root of the square of the weight in kilograms by the constant 12.312, he obtained the surface area in square decimeters.

The constant should be 0.12312 so that the result will be in square meters. As a matter of fact, everyone places the decimal point by inspection, since the surface area of all ordinary adults is between 1 and 2 square meters. The calculation of the formula $12.312\sqrt[3]{\text{Kg.}^2}$ is not difficult if logarithms are used. The logarithm of the weight in kilograms is multiplied by 2, the result divided by 3, and this result added to the logarithm of 0.12312. The antilogarithm of the final result gives the surface area in square meters.

Meeh's work was ingenious and painstaking, but he must have allowed the papers with which he covered the body to fit very loosely, as practically all subsequent investigators have found his estimations too large. Meeh himself realized some of the limitations of his formula, since he applied it only to the adults and older children. For infants he used the constant 11.9 and for various species of animals still other constants.

Bouchard^{1,2} later measured several individuals and devised a complicated formula which has been simplified by means of graphs published by Broca³ and Faillie.⁴ This method has not been extensively employed though Faillie recommended it highly and Takahira checked its accuracy. Sicheff⁵ in 1902 measured 24 children and found that the constant for Meeh's formula should be 10.7. Lissauer⁶ one year later published the measurements of 12 dead babies, most of them atrophic. Lissauer's constants, according to the Meeh formula, were between 8.9 and 12.4, and he chose 10.3 as the best for general use with children. The results of Fubini and Ronchi,⁷ as well as those of Bouchard, indicated that Meeh's constant of 12.3 was also too high for adults. In spite of all this work Meeh's formula remained the standard

¹ Bouchard: *Compt. rend. Acad. d. Sc.*, 1897, **124**, 845.

² Bouchard: *Traité de pathologie générale*, Paris, 1900, **3**, 200, 384.

³ Broca: *Precis de physique médicale*, 1907, p. 47.

⁴ Faillie: *Arch. Int. Med.*, 1925, **35**, 626.

⁵ Sicheff, A.: *Inaugural Dissertation*, St. Petersburg, 1902. Quoted by Gundobin: *Die Besonderheiten des Kindesalters*, Berlin, 1912.

⁶ Lissauer: *Jahrb. d. Kinderheilk.*, 1902, **58**, 392.

⁷ Fubini and Ronchi: *Moleschott's Untersuchungen zur Naturlehre*, 1881, **12**, 1.

for about thirty-seven years. Howland and Dana¹ and others devised formulas based largely on Meeh's measurements, but they never came into general use.

When the staff of the Russell Sage Institute of Pathology decided to publish their calorimeter results in terms of calories per square meter of body surface it seemed rather ridiculous to measure the calories within 1 or 2 per cent and then divide by a factor which might contain an error of 10 or 20 per cent. Delafield Du Bois,² an electrical engineer, was persuaded to undertake the laborious task of repeating Meeh's work. After much experimentation he devised the following improvements on the methods previously used. The subject was dressed in tightly-fitting underwear, with thin socks, thin cotton gloves, and a section of the leg of a knitted undersuit over the head and neck. On this groundwork strips of manila paper were pasted until a flexible but inelastic mould of the body was completed. This was then marked out in the different regions of the body according to bony landmarks and removed by means of curved bandage scissors. The mould of each region of the body was then given a coat of melted paraffin and cut into small pieces which would lie flat. These were then placed in a large printing frame over sheets of weighed photographic paper and prints made in the sun. The unexposed paper under the pieces of mould were cut out and weighed, thus making it an easy matter to determine the surface area of each part of the body. The method seems to have been very accurate, since it was applied to a large bowling-ball and the results differed by only 0.13 per cent from the surface area as calculated from the average diameter. Five subjects of widely differing shapes were so measured and the next year five more were added to the list by Sawyer, Stone and E. F. Du Bois.

Pfaundler³ in 1916 used a similar method for infants. He called attention to the fact that you could make a great difference in the area of an animal's skin by stretching and that if the human skin be examined under a microscope it shows many small folds. He emphasized the necessity of speaking not of the absolute surface but rather of the surface according to a certain method.

¹ Howland and Dana: *Am. Jour. Dis. Child.*, 1913, 6, 33.

² Du Bois, D., and Du Bois, E. F.: *Clin. Cal. 5, Arch. Int. Med.*, 1915, 15, 868.

³ Pfaundler: *Ztschr. f. Kinderheilk.*, 1916, 14, Heft. ½, 1.

The actual measurement of the surface area of an individual by means of paper moulds is obviously too laborious for general use and the Sage investigators endeavored to find some formula that was accurate yet fairly simple. We have seen that the body had been divided into various regions. These were head, arms, hands, trunk (including neck), thighs, legs and feet. Each of these regions was measured in several places to find the average or characteristic length and circumference of each region. By calculation it was possible to determine the measurements that gave the best results in the 5 subjects. Having selected the best average length and circumference, these were multiplied and the result corrected by a factor calculated from the actual measurements.

The sum total of all the parts of the body gave the total surface area. The measurements were made with the subject lying on a flat table and required only three or four minutes with an equal time for the necessary calculations. This so-called "linear formula" of D. Du Bois was checked up a year later by Sawyer, Stone, and E. F. Du Bois¹ on 5 additional subjects measured in the same manner and the average error found to be 1.3 per cent. The general principle of this method is by no means new. Abernethy in 1793 and Roussy² in 1911 employed the average length and breadth of the various parts of the body to calculate the surface but apparently did not correct by factors. Roussy's publication, curiously enough, is scarcely mentioned in the literature and was not known in this country until described by Murlin.³

The linear formula seems to be the only one that can be applied with any degree of accuracy to people of widely differing body form. It is obvious that a tall, thin man may have exactly the same weight as a short, fat man, yet have a much larger surface area. The linear formula obviates this, since it measures the length and circumference of each part of the body. It showed an error of -2.9 per cent in the case of a thin baby, $+0.1$ per cent in a very tall, thin man, and $+2$ per cent in a short and almost globular woman weighing 93 kilograms (205 pounds).

¹ Sawyer, Stone and Du Bois, E. F.; Clin. Cal. 9, Arch. Int. Med., 1916, 17, 855.

² Roussy: Compt. rend. Acad. d. sci., 1911, 153, 205.

³ Murlin: Endocrinology and Metabolism, New York, D. Appleton & Co., 1922, vol. 3.

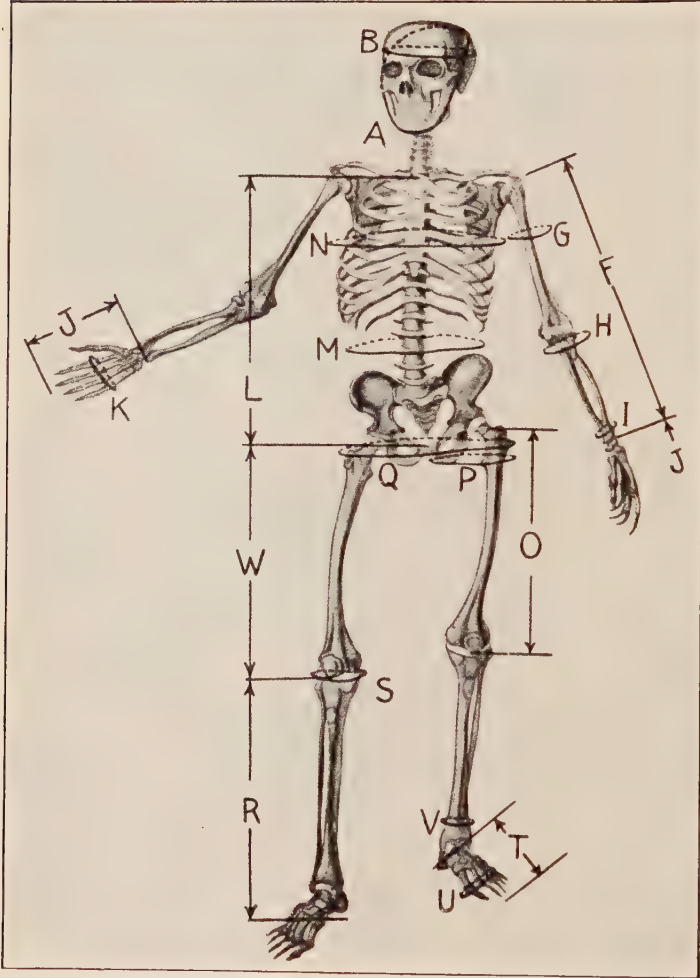


FIG. 16.—Measurements used in "linear formula."

TABLE 16.—MEASUREMENTS AND CONSTANTS FOR LINEAR FORMULA (MEASUREMENTS TAKEN WITH SUBJECT LYING ON A FLAT SURFACE).

HEAD: AB 0.308.

A—Around vertex and point of chin.

B—Coronal circumference around occiput and forehead, just above eyebrows.

ARMS: $F(G + H + I) \cdot 0.611^1$.

F—Tip of acromial process to lower border of radius, measured with forearm extended.

G—Circumference at level of upper border of axilla.

H—Largest circumference of forearm (just below elbow).

I—Smallest circumference of forearm (just above head of ulna).

HANDS: JK 2.22.

J—Lower posterior border of radius to tip of second finger.

K—Circumference of open hand at the metacarpo-phalangeal joints.

TRUNK (including neck and external genitals in the male, breasts in female):

$L(M + N) \cdot 0.703$.

L—Suprasternal notch to upper border of pubes.

M—Circumference of abdomen at level of umbilicus.

N—Circumference of thorax at level of nipples in the male and just above breasts in the female.

THIGHS: $O(P + Q) \cdot 0.508$.

O—Superior border of great trochanter to the lower border of the patella.

P—Circumference of thigh just below the level of perineum.

Q—Circumference of hips and buttocks at the level of the great trochanters.

Or:—THIGHS: $W(P + Q) \cdot 0.552$.

W—Upper border of pubes to lower border of patella (measured with legs straight and feet pointed antero-posteriorly).

P—As above.

Q—As above.

LEGS: RS 1.40.

* R—From sole of foot to lower border of patella.

S—Circumference at level of lower border of patella.

FEET: $T(U + V) \cdot 1.04$.

T—Length of foot including great toe.

U—Circumference of foot at base of little toe.

V—Smallest circumference of ankle (just above malleoli).

NOTE.—The constants for arms, thighs, etc., when multiplied by the measurements of one side give the surface area for both sides. To find total surface area add the seven parts.

¹ Factor 0.558 if F is measured over olecranon with forearm flexed.

In a later publication D. Du Bois¹ made some slight corrections in the original linear formula and worked out a new "height-weight formula" based on height and weight alone. This is expressed as $A = W^{0.425} \times H^{0.725} \times C$, A being the surface area, W the weight in kilograms, H the height in centimeters, and C a constant, 71.84. This can also be expressed in the terms

$$A = W^{2.35} \times H^{1.38} \times C$$

and can be solved by logarithms as follows:

$$\text{Log. } A = \text{Log. } W \times 0.425 + \text{Log. } H \times 0.725 + 1.8564;$$

1.8564 is a constant equal to Log C.

In order to avoid this calculation a chart (Fig. 17) was constructed so that the approximate area could be determined at a glance. The ordinates represent the height, the abscissæ, the weight in kilograms. The point of intersection of the proper lines is found for any given subject and the surface area read off by interpolation between the curved lines. In this chart it is necessary to estimate the second decimal place by the distance from the nearest curved lines. In some recent publications this chart has been printed with subdivisions for each kilogram of weight, centimeter of height, and hundredth of a square meter. This causes a confusion of lines and a confusion of ideas as to the accuracy of the method. A variation of 1 kilogram in weight has slight significance; the height varies a centimeter during different times of day. The surface area method is not accurate in the second decimal place. The original chart was made to show that the second decimal place is merely an estimation by this or any other method.

This formula has been expressed in nomographic form by Wilson and Wilson,² Boothby and Sandiford,³ and by Janet.⁴ Fig. 18, p. 120 shows the nomogram of Boothby and Sandiford. The surface area can be found by placing a ruler at the proper readings for height and weight. This will cross the

¹ Du Bois, D., and Du Bois, E. F.: Clin. Cal 10, Arch. Int. Med., 1916, 17, 863.

² Wilson, C. M., and Wilson, D.: Lancet, 1920, 199, 1042.

³ Boothby and Sandiford, R. B.: Boston Med. and Surg. Jour., 1921, 185, 337.

⁴ Janet, H.: Le métabolisme basal en clinique, Paris, Jouve & Co., 1922.

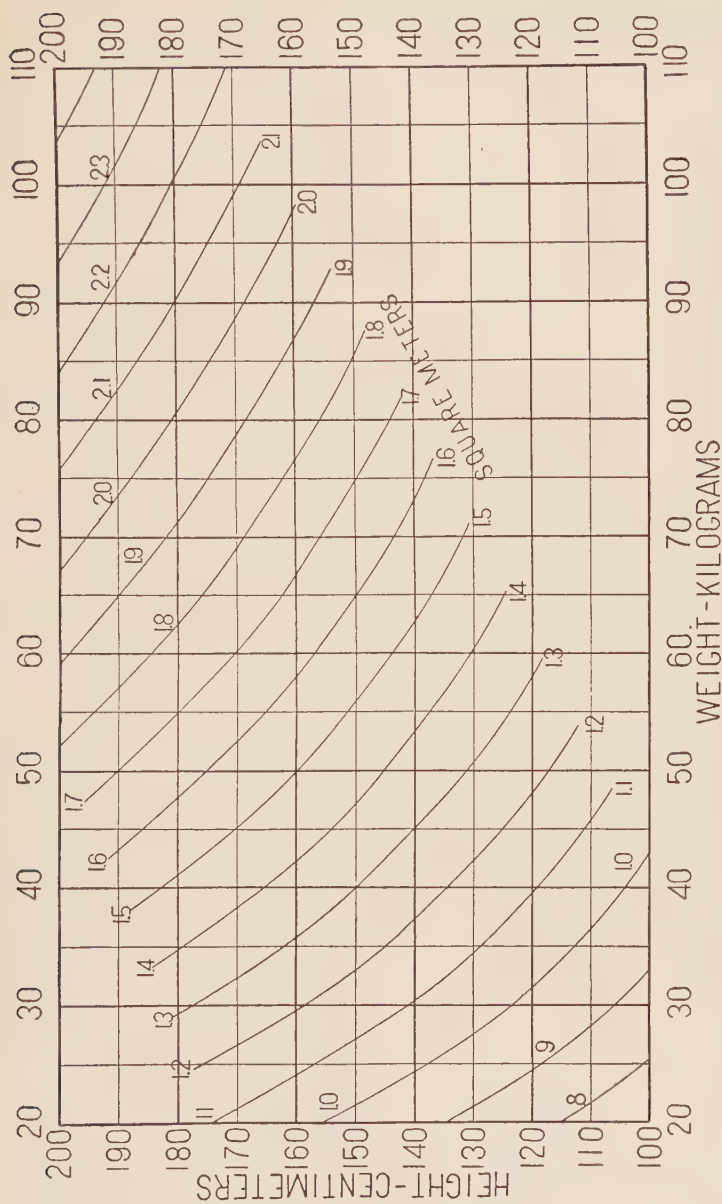


Fig. 17.—Chart for determining surface area of man in square meters from weight in kilograms (Wt.) and height in centimeters (Ht.) according to the formula: Area (sq. Cm.) = $\text{Wt.}^{0.725} \times \text{Ht.}^{0.725} \times 71.84$.



FIG. 18.—Chart for basal metabolic rate determinations. (Copyright, 1920, by W. M. Boothby and R. B. Sandiford.)

center line at a point which gives the reading for the surface. Stoner¹ has published some long tables which give the surface to the third decimal place though only the first two significant figures are strictly accurate according to the original work on this formula.

The formula $A = W^{0.425} \times H^{0.725} \times 71.84$ seems rather complicated, but when applied to the 10 subjects whose surface area was measured in moulds it gives better results than any other formula, the average error being 1.7 per cent and the largest error for an adult 2 per cent. The formula $A = W^{\frac{1}{3}} \times H^{\frac{1}{3}} \times 167.2$ was almost as good, the average error being 2.2 per cent, but it was -5.8 per cent from the actual measurement of a fat woman. The formula $A = W^{\frac{1}{3}} \times H \times 25.6$ was not so good, showing an average error of 3.3 per cent. Meeh's formula $A = W^{\frac{1}{3}} \times 12.312$ has an average error of about +15 per cent. With a constant of 10.79 the average in the 10 measured cases is 5.5 per cent, with a maximum of 16 per cent in the case of the fat woman.

In the 10 adult cases actually measured the linear formula and height-weight formula showed average errors of about 1.7 per cent. The linear formula showed slightly better results in the majority of cases, but there does not seem to be enough difference to make it worth while to take all the measurements unless the individual has an unusual body shape.

Fortunately studies by Wörner² and Takahira³ permit us to check the accuracy by means of data from other laboratories. Wörner who apparently did not have access to the American literature made direct measurements of 17 subjects, 12 of them being adults, using a method almost exactly the same as that of D. Du Bois. Wörner believed that there was no relationship between body weight and length and surface but if we apply the height-weight formula to his subjects we obtain an average deviation of 1.45 per cent with regard to sign and 3.53 per cent without regard to sign. The greatest divergence is 9.3 per cent.

Takahira's work is even more valuable since he has rechecked the Sage measurements in every possible manner.

¹ Stoner: Jour. Lab. and Clin. Med., 1926, 11, 355.

² Wörner: Ztschr. f. d. gesamt. exper. Med., 1923, 33, 510.

³ Takahira: Rep. of Metab. Lab. Imper. Govt. Inst. for Nutrition, Tokyo, 1925, vol. 1, No. 1, p. 61.

The surface of 10 Japanese men was determined by means of a mould of very thin paper, cut into flat pieces and mapped out by a planimeter. This method was tested on a rubber ball of known diameter and 10 closely agreeing figures obtained though they ranged 1.1 per cent below the theory. Knowing the actual areas of the ten men he tested the various surface area formulas as is shown in Table 15. Surprisingly close

TABLE 15.—COMPARISON OF ACTUAL MEASUREMENT WITH RESULTS CALCULATED ACCORDING TO VARIOUS FORMULAS (TAKAHIRA).

			Av.		Marc.
Meeh	$A = W^{\frac{2}{3}} \times 12.3$	+	9.26	+	12.38
_____	$A = W^{\frac{2}{3}} \times 11.15$	=	1.91	=	4.21
Lissauer	$A = \frac{W}{H} \times 48.84$	=	4.32	=	9.22
_____	$A = H \times W^{\frac{1}{2}} \times 25.47$	=	1.37	=	3.53
Du Bois and Du Bois	$A = H^{\frac{1}{2}} \times W^{\frac{1}{2}} \times 167.2$	=	1.56	=	3.16
_____	$A = H^{\frac{1}{2}} \times W^{\frac{1}{2}} \times 169.2$	=	1.14	=	2.82
Du Bois and Du Bois	$A = H^{.725} \times W^{.425} \times 71.84$	=	1.28	=	3.50
_____	$A = H^{.725} \times W^{.425} \times 72.46$	=	0.95	=	2.64
Stöltzner and Miwa	$A = \frac{U H W}{U^4 W^4 U^2} \times 40.42$	=	1.78	=	3.62
Bouchard	$A = 0.386LH + 8.239 \frac{W}{L}$				
	$+ 3.162H \frac{W}{\pi H}$	=	1.12	=	2.91
Linear formula	Geometrical method of calculation	=	2.24	=	5.43

agreement was found using several different methods particularly if the constants were changed. The best results for Japanese men were obtained by using the Sage height-weight formula with the constant 72.46 instead of 71.84. By means of a long series of calculations he tested the various exponents for height and weight and noted a slight improvement if he employed the following formula:

$$H^{0.718} \times W^{0.427} \times 74.49 \text{ instead of } H^{0.725} \times W^{0.425} \times 71.84$$

It is interesting to note that Takahira found the Sage formula averaged 0.9 per cent too low, Wörner 1.45 per cent too high.

Benedict¹ has devised an ingenious method of estimating the surface area by taking photographs of the front and side view of his subjects with a meter stick in exactly the same focus. By means of a planimeter he computes the areas of

¹ Benedict, F. G.: Am. Jour. Physiol., 1916, 41, 275.

the silhouettes and multiplies by the proper constants. In the case of the side view with hands extended the constant 5.02 gives extraordinarily accurate results and also furnishes a permanent record of the individual's body shape. Using the linear formula to find the surface area of 20 subjects, he obtained results which were all within 5 per cent, the average divergence being +1.6 per cent. Thirteen of the 20 showed an agreement within 1 per cent.

Roussy¹ seems to have anticipated the general principles of this method also. A similar procedure is described in his publication which was unknown to German and American writers. Benedict is certainly the first to call our attention to the importance of the silhouette. It is, of course, an accident that the constant is almost exactly 5 for the side view of the body. We must remember that if the metabolism is proportional to surface area it must also be proportional to the silhouette. This photographic method seems to be fundamentally sound and it should prove to be of considerable value. It recommends itself to physiologists who wish to measure the surface of wild animals in captivity.

The original height-weight chart was not constructed to show the area of subjects weighing less than 20 kilograms (44 pounds), but a new chart has been made for children (Fig. 19). Only one small child was actually measured in the Sage laboratory, a poorly nourished girl, aged twenty-one months, weighing 6.27 kilograms, the average weight for an infant of four months. In her case the error in the height-weight formula was +5.1 per cent, in the linear formula -2.9 per cent.

Pfaundler² measured the surfaces of 12 infants. He covered the body with sticky plaster which would stretch very little, then painted the surface and cut up the mould so that it could lie flat and be measured by a planimeter. His subjects were very small, their weights ranging between 2 and 6 kilograms, and their areas between 0.16 and 0.29 square meters. The surfaces as estimated from the height-weight formula in Fig. 19 average 1.5 per cent lower than Pfaundler's actual findings. The average diverging is 4 per cent, the maximum about 7 per cent. Pfaundler quotes a series of similar measurements made in his clinic by Kastner in 1912

¹ Roussy: *Compt. rend. Acad. d. sci.*, 1907, 145, 139.

² Pfaundler: *Ztschr. f. Kinderheilk.*, 1916, 14, Heft 3, 1..

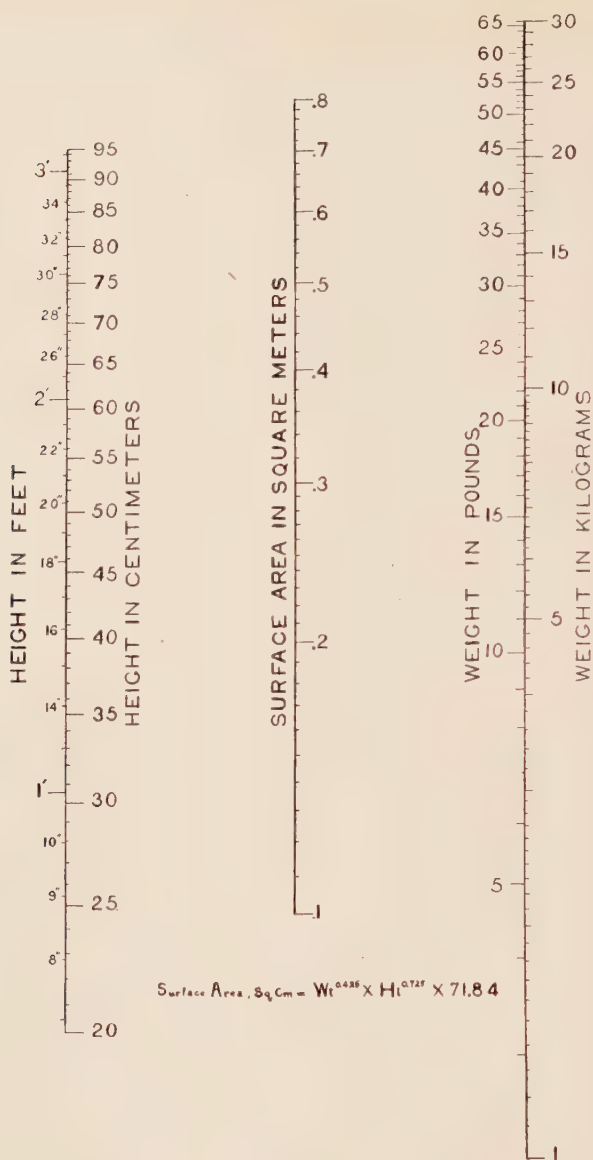


FIG. 19.—Nomogram made by R. R. Hannon for estimating the surface areas of children according to the formula of Du Bois and Du Bois. Place a ruler over the proper height and weight. Read off the surface area at the point the ruler crosses the middle line.

on very thin babies. These earlier results which do not seem to be as trustworthy as Pfaundler's average 15 per cent higher than the Sage height-weight formula. Wörner in his series measured 5 children between the ages of five and seventeen years and the estimations from the height-weight chart average only 0.7 per cent too low, the greatest error being 5 per cent.

Benedict and Talbot¹ who did not use moulds for their children compared the surfaces as calculated from the Sage linear formula and the Sage height-weight formula and obtained reasonably satisfactory agreement down to 20 kilograms of weight and found that the linear formula and the Lissauer formula $10.3 \sqrt[3]{W_2}$ agree fairly well for children. In their monograph they give a table for constants for the Lissauer formula at different ages and also a table to obtain the surface from the weight alone. There are theoretical objections to this since height is certainly a factor in determining the surface. Faber and Melcher² have measured the surfaces of 100 newborn babies according to the linear formula and have suggested that for infants the height-weight formula be modified and a K of 78.50 used instead of K 71.84. The higher constant gives results which agree rather closely with the linear, the average divergence being only 2.5 per cent. Irene Sandiford³ has studied the surface of the human fetus by means of the linear formula finding that their results agree fairly closely with the height-weight formula and the Lissauer formula of $10.3 \sqrt[3]{W_2}$. She has devised a graphic method of estimating the surface of the human fetus from the lunar month of gestation. The accuracy of this will not be fully tested until the surfaces of fetuses are actually measured and this is an almost impossible task.

The measurements of Pfaundler and Wörner and the close agreement with the linear method indicate that the height-weight formula may be applied to infants with almost the same degree of accuracy as in the case of adults. The surface area formulas suggested by Benedict and Talbot and Faber and Melcher are based on indirect determinations whose accuracy has not yet been tested.

¹ Benedict and Talbot: Carnegie Institution of Washington Publication No. 302, 1921, p. 61.

² Faber and Melcher: Proc. Soc. Exper. Biol. and Med., 1921, 19, 53.

³ Sandiford, I.: Jour. Biol. Chem., 1924, 62, 323.

Boothby and Sandiford^{1,2} in a most ingenious manner have turned the Harris-Benedict multiple prediction formula into a method for estimating the surface area and have obtained results which are surprisingly accurate. For an interesting analysis of the various formulas the reader is referred to their papers.

Dreyer, Ray and Walker³ have found that blood volume, the cross-section of the aorta and of the trachea are all proportional to the body surface. They find that surface area is proportional to the weight raised to the 0.70 or 0.72 power ($W^{0.70}$ or $W^{0.72}$) instead of to the two-thirds power ($W^{0.666}$) employed by Meeh.

Bardeen⁴ has made an extremely interesting study of the height-weight index of the body from birth to old age. This factor expresses the part of a space equal to the cube of the height occupied by the volume of the body. By means of picture diagrams he shows clearly that the infant body occupies a much greater proportion of such a cube than the youth and the youth more than the old man. For instance, the index is about 0.92 at birth, 0.42 at the age of eighteen, and 0.52 in old age. If we simply divide the weight in grams by the height in centimeters, assuming a specific gravity of 1000, the quotient gives us the average cross-section in square centimeters of an object as long as the body and of the same volume. This elongated object may be conceived of as circular or square in cross-section, the latter naturally having the larger surface area. Bardeen calculates the surface of such an elongated block as follows:

$$S = K \left(\frac{2W}{H} + 4H \sqrt{\frac{W}{H}} \right)$$

in which S equals surface area, W is the weight in grams, H the height in centimeters, and K is a constant. In this formula $\frac{W}{H}$ gives the surface area of each end of the block $H\sqrt{\frac{W}{H}}$ the surface area of one side. K , as determined from the subjects measured by Du Bois and Du Bois, was 1.15 for a very fat woman and 1.29 for a tall, thin man. The average

¹ Boothby and Sandiford, I.: *Jour. Biol. Chem.*, 1922, **54**, 767, 783.

² Sandiford, I.: *Ibid*, 1924, **62**, 323.

³ Dreyer, Ray and Walker: *Proc. Roy. Soc.*, 1912-1913, **86**, 39, 56.

⁴ Bardeen: *Carnegie Institution of Washington Publication No. 272*, 1920.

K of 1.237 gave fairly close estimations of the different subjects.

A detailed study of the relationship of height and weight of school children will be found in an excellent monograph by Baldwin.¹ The two publications of Bardeen and Baldwin furnish extensive bibliographies of the many works on the average heights and weights of different races, and the reader who is interested in this subject can follow it from the investigations of the pioneer Quetelet down to the present time. Harris and Benedict also give many references to measurements of groups of normals.

The most valuable standard would seem to be the medico-actuarial mortality investigation of 1912.² Here we have collected an enormous number of measurements of Americans accepted for life insurance and therefore presumably normal.

¹ Baldwin; United States Bureau of Education Bulletin No. 10, 1914.

² Association of Life Insurance Medical Directors and the Actuarial Society of America, New York, 1912.

CHAPTER VII.

FACTORS WHICH INFLUENCE THE NORMAL BASAL METABOLISM.

IN practically all laboratories the metabolism is measured in the morning twelve to fourteen hours after the last meal with the subject lying motionless. Under such conditions we obtain what is usually called the basal metabolism or "Grundumsatz" of Magnus-Levy. Strictly speaking this is not the lowest or basal metabolism since we can obtain lower figures during prolonged undernutrition and during profound sleep. For this reason Krogh¹ uses the term "standard metabolism" which though perfectly rational has never come into general usage. F. G. Benedict employs the expression "postabsorptive" to denote the fact that the tests are made after the absorption of food has ceased. Plummer and Boothby have recently adopted the phrase "basal metabolic rate." This seems to have caught hold in this country as it expresses the idea of chemical processes taking place within the body at a certain standard velocity. The only objection to this term is that it adds a word which is not strictly necessary and we hesitate in making two words grow where one grew before.

The basal metabolism is fairly constant in a given individual and in similar individuals of the same species. We do not know the exact cause of this but we are naturally reminded of a similar constancy in many other physiological measurements. The temperature of normal men shows surprising uniformity, the pulse rate and blood-pressure do not present great variations. In the blood there are comparatively small changes in the hemoglobin and cell count. The glucose and chloride content under standard conditions are fairly uniform and the hydrogen-ion concentration is fixed within narrow limits. We probably inherit these from remote ancestors and they have apparently changed less than our external forms during thousands of centuries.

¹ Krogh: *Respiratory Exchange of Animals and Man*, New York and London, Longmans, Green & Co., 1916.

There are many factors which affect this basal metabolism such as age, sex, size, etc., and these will be discussed at length. Before doing this, however, we must select certain standards and methods of expression.

It so happens that we know a great deal about the basal metabolism of young men. They make ideal experimental subjects, much better than dogs or guinea-pigs, and they are always available in laboratories. As a matter of fact, the science of metabolism has been founded on the very bodies of medical students and physiologists. There is a large homogeneous group of normal controls between the ages of twenty and forty years. We cannot rule out the age factor entirely during these two decades, but there is much evidence to show that man changes comparatively little at this time of life. For these reasons we shall base our discussion on the metabolism of young men.

How shall we express our results? Most of the pioneers spoke in terms of CO_2 but we have seen in the previous chapters that the elimination of this gas furnishes a poor gauge of the heat production. The oxygen is a better indicator but if we leave the calculations at this stage there may be frequent errors of 2 per cent and sometimes 3 or 4 per cent. The error of calculation can be reduced to about 1 per cent by reckoning the calories from the oxygen and the respiratory quotient so we shall use this standard wherever possible. It gives the impression of laziness if we leave the calculations in the less exact and less significant stage of mere volumes of carbon dioxide or oxygen. We must choose also a standard of time. Much of the older literature is written in terms of calories per twenty-four hours. This was perfectly rational when the experiments were made in large respiration chambers in which the subjects lived for one or more days. The results gave a good idea of the calories required for the maintenance of the individual, but they were not basal. Basal conditions cannot be held for more than a few hours at a time. Our modern experimental periods are from ten minutes to two or three hours and it seems rational to use the hour as a standard. We can, for instance, figure for the day a certain number of hours of basal metabolism, a certain number for the effect of meals, etc. The minute as a unit makes it necessary to deal with small fractions and large multiplications and it seems advisable to abandon this in spite of its adoption by

the Zuntz school. We therefore express our results according to calories per hour.

We now have a unit for the individual. How constant will this basal metabolism remain from hour to hour, from day to day and from year to year?

For a given man the variations are not very large and our experimental results reflect three variables. The first consists in the true variation of the basal metabolism of the individual. The second is the experimental error of the apparatus which may be 1 per cent or more. The third may be caused by any undiscoverable slight extraneous factor which modifies the metabolism of the subject, such as physical exhaustion on the previous day or unsuspected illness or unconscious increase in the muscular tension. The sum total of all these shows us the variations in our measurements and this is of tremendous importance from a practical standpoint when we attempt to interpret the results of any one determination. We can, however, rest assured that the actual variations of the basal metabolism are smaller than the variations of the measurements.

In a large group of normal men of the same age and size almost all of the determinations of the basal metabolism will fall within 10 per cent of the average. There will be a few variations between 10 and 15 per cent. Differences of about the same magnitude are found in almost every large series of tests made on the same man over a long period of time. This was well shown by Magnus-Levy¹ on a man who was studied from May 7, 1891 to April 5, 1893. The average oxygen consumption was 220 cc per minute and the variations were between -7 per cent and +10.5 per cent. Magnus-Levy excluded from this average two days, June 27 and 29, 1891, on which the figures were 22 per cent above the average. The cause of the unusually high metabolism at this time was not clear but the tests on those two days certainly did not represent the man's normal basal level. The moral of this, as pointed out by Magnus-Levy, is that we cannot trust implicitly the test made on any one day. Johansson² who measured only the carbon dioxide production, found but slight changes from day to day and from hour to hour during the day. Taking the periods during the day when there was

¹ Magnus-Levy: *Arch. f. d. ges. Physiol.*, 1894, 55, 1.

² Johansson: *Skand. Arch. f. Physiol.*, 1898, 8, 85.

complete muscular relaxation, the greatest differences amounted to about 10 per cent. F. G. Benedict¹ has published a table showing the extreme variations of all the subjects studied in his laboratory over periods of more than five days. The results are expressed in terms of variation in oxygen above the minimum and are therefore somewhat larger than if they had been given in terms of deviation from the mean. Out of the 35 subjects as well as we can calculate from the data given, all but 3 showed extreme variations within 10 per cent of their average figures while 21 were apparently always within 7 per cent. The greatest variation, 31.3 per cent above the minimum was found in a man on whom 211 experiments had been made. A striking uniformity was seen in one man studied 103 times whose maximum oxygen consumption exceeded his minimum by only 8.2 per cent. Benedict and Carpenter² have given in greater detail the data of 4 of these subjects. On the basis of oxygen consumption the mean variations are as follows: H.L.H. 3.7 per cent, L.E.E. 3.3 per cent, K.J.M. 2.9 per cent, M.A.M. 4 per cent. Experiments on these and other subjects made during many different months of the year extending through several years showed no significant change in metabolism with the season of the year. Hafkesbring and Collett³ observing their own metabolism in Texas noted that the basal figures were about 5 per cent higher in cold than in hot weather. Gessler⁴ found his own metabolism was about 7 per cent above his average in winter and about 6 per cent below in summer. If this applies to many subjects it is of great importance since it would oblige us to use different standards in winter and in summer. Perhaps it is only a coincidence but most of the high values given in Table 18 were obtained in the cold months and at low values in the warm months.

It is apparently impossible to detect any consistent change during the day. Benedict and Carpenter made a large number of studies extending through the morning hours and apparently established this fact very clearly. The afternoon experiments are not so numerous but they give no hint of diurnal fluctuations. We might expect a small change with

¹ Benedict: *Jour. Biol. Chem.*, 1915, 20, 263 (Table 4, p. 291).

² Benedict and Carpenter: *Carnegie Institution of Washington Publication No. 261*, 1918, p. 115.

³ Hafkesbring and Collett: *Am. Jour. Physiol.*, 1924, 70, 73.

⁴ Gessler: *Plüger's Arch.*, 1925, 207, 370.

the rising temperature in the afternoon but this may be offset by a slight diminution of the influence of the meal taken the previous evening.

We are fortunate in having at our disposal a series of metabolism determinations on the two veteran experimenters Zuntz and Loewy.¹ These show a gradual decline with advancing years until the period of undernourishment during the war caused a marked drop in the caloric requirement. This will be discussed later. A striking uniformity is seen in the normal control E. F. D. B. studied in the Sage calorimeter at intervals for eleven years (Table 18.)

TABLE 18.—BASAL METABOLISM OF E. F. D. B.² (HEIGHT, 178-178.8cm.)

Date.	Year.	Age Years.	Weight (kg.).	Surface Ht.-Wt. (sq m.).	Calories.		Variation from average p. c.
					per hour.	Per sq. m. per hour.	
Mar. 13, 1913	.	30	73.6	1.91	77.6	40.6	+7.7
May 17, 1913	.	..	75.5	1.95	73.2	38.1	+1.1
Mar. 30, 1914	.	31	74.3	1.93	74.1	38.4	+1.8
May 18, 1914	.	..	73.7	1.92	71.3	37.2	-1.3
May 6, 1915	.	32	74.6	1.93	71.8	37.2	-1.3
May 7, 1915	.	..	74.2	1.93	68.6	35.5	-5.8
Apr. 12, 1916	.	33	76.5	1.94	75.4	38.8	+2.9
Apr. 25, 1916*	.	..	77.3	1.95	73.2	37.5	-0.5
Dec. 18, 1916	.	34	73.9	1.90	76.2	40.1	+6.4
May 10, 1922*	.	39	78.0	1.97	68.6	34.8	-7.7
Oct. 7, 1923	.	41	74.7	1.93	70.8	36.7	-2.6
Apr. 10, 1924†	.	..	75.0	1.94	71.7	37.0	-1.9
					37.7		

* 1 hour experiment.

† Benedict-Roth apparatus.

These facts have a most important bearing on all metabolism experiments. They demonstrate a certain standard heat production for a given subject under the usual basal conditions of complete muscular relaxation twelve to twenty hours after the last meal. We can use this as a base line for the study of various superimposed factors such as food or drugs or muscular exercise. In our interpretation of the results it is necessary to remember that the base line is not absolutely fixed and the experiments should be repeated on several different subjects or on the same subject several times in order to eliminate the effects of spontaneous fluctuations in metabolism. In some laboratories with carefully selected subjects the variations are extremely small from day to day if the experimental periods are long or if averages are taken

¹ Zuntz and Loewy: Berl. klin. Wchnschr., 1916, 53, 825; Biochem. Ztschr., 1918, 90, 244.

² Lusk and Du Bois: Jour. Physiol., 1924, 59, 213.

from a large number of short periods. Every laboratory should determine for itself the extent of these variations.

All who work with basal metabolism feel the necessity of checking from time to time the accuracy of their experimental procedure. The usual tests for leaks and duplicate analyses are not enough. Alcohol checks are the best but at present are difficult except with closed respiration chambers. For small apparatus one of the most valuable procedures is to make repeated determinations on some normal control who will be available over a period of several years. Any large variation will make the operator suspect trouble with the apparatus.

Having determined the constancy of the metabolism in a single man, it is now important to compare different individuals. We can base our comparisons on the total heat production, but it would be obviously unfair to match a large man with a small man since the former would have a much greater metabolism. On the other hand, if we spoke in terms of calories per kilogram, the small man would give the higher figure. We might select for the determination of certain factors groups of men of exactly the same age, stature and weight, but this would be a laborious and rather difficult procedure. Experience has shown that the most satisfactory basis for comparison is the heat production per square meter of body surface. The basal metabolism of various warm-blooded animals is, within certain limits, proportional to their surface area. While the level of metabolism may very well be caused by some other factor which is proportional to surface area, this other factor is uncertain and cannot be measured directly. Therefore it seems advisable to use the surface as a standard in our discussions.

It has long been known that metabolism is high in childhood. This was clearly demonstrated by Magnus-Levy and Falk¹ in 1899.

In 1915 Du Bois² studied some boys in the Sage calorimeter and grouping his results with those of previous investigators constructed a curve showing the sudden rise in metabolism during the first year in life, the peak in early childhood and the gradual decline until the period of growth

¹ Magnus-Levy and Falk: *Arch. f. Anat. u. Physiol.*, 1899, Suppl., p. 314.

² Du Bois: *Jour. Washington Acad. Sci.*, 1916, 6, 347; *Clin. Cal.* 12, *Arch. Int. Med.*, 1916, 17, 887; *Am. Jour. Med. Sci.*, 1916, 151, 781.

was ended. This is given on page 199. While the actual level of the line is probably too high between the ages of two and fourteen years and the secondary rise at the period just before puberty is still debatable the general contour of the curve has been substantiated by subsequent studies in many laboratories.

In order to obtain a more complete picture of the age curve we should start with fetal life. The subject has been well reviewed by Murlin.¹ It has been shown that, per unit of mass, the metabolism in the embryos of the lower animals is

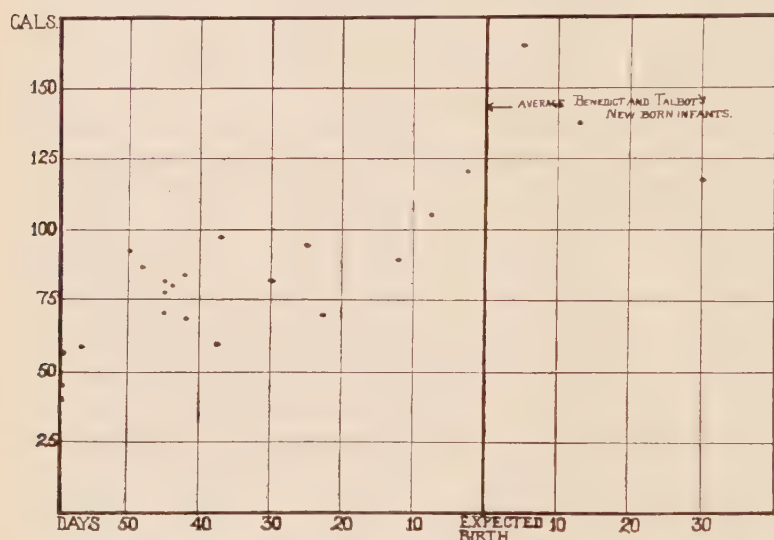


FIG. 20.—Premature infants. Total calories in relation to expected birth. (Talbot.)

greater than in the adult tissue, apparently being greatest at the time when the work of differentiation is most active. The experiments on mammalian embryos are technically difficult and as yet not convincing.

The metabolism of premature infants has been studied by Talbot, Sisson and their associates.² The series includes 21 babies all at least four to ten weeks premature. Their

¹ Murlin: *Am. Jour. Physiol.*, 1910, **26**, 134; *Endocrinology and Metabolism*, New York, D. Appleton & Co., 1922, **3**, 616.

² Talbot and Sisson: *Proc. Soc. Exper. Biol. and Med.*, 1922, **19**, 309. Talbot, Sisson, Moriarty and Dalrymple: *Am. Jour. Dis. Child.*, 1922, **24**, 95; 1923, **26**, 29.

weight curves were, as a rule, stationary for seven to ten days and after that there was satisfactory development. Their results are shown in Figs. 20, 21, 22.

It will be seen from these charts that the heat production is extremely low. It gradually increases with age, the line tending to run parallel with that of normal babies, although at a lower level. Talbot found that muscular activity sometimes increased the metabolism as much as 40 per cent. He observed the relationship of caloric intake to growth and found that there was no gain in weight until the premature

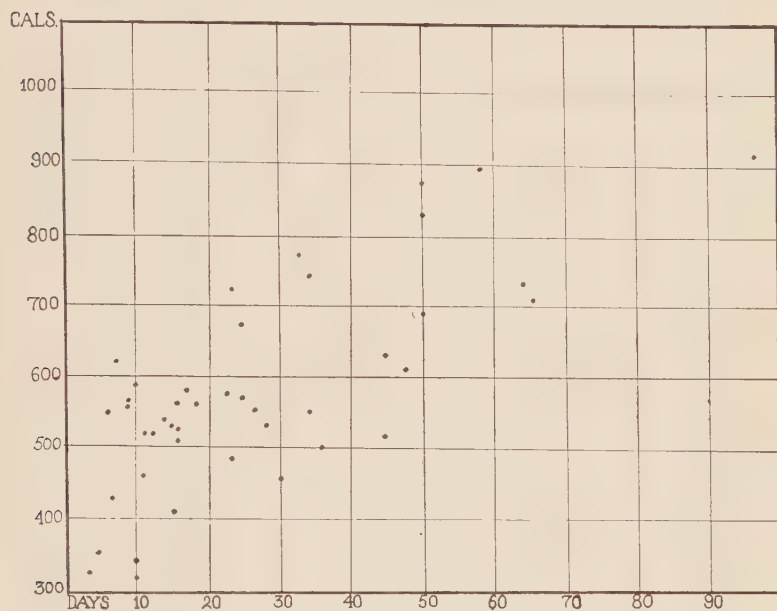


FIG. 21.—Premature infants. Calories per square meter. (Talbot.)

babies were able to digest about 200 calories a day. It does not seem to be necessary to make much allowance for muscular activity, and the loss of calories in the excreta is usually less than 10 per cent of the food intake, although it may be 20 per cent if there are four or five large curdy stools a day.

Talbot's work has been confirmed by Marsh and Murlin¹ who studied premature and undersized infants. They found that premature babies produced on the average 6.48 calories an hour or 26.25 calories per square meter per hour according

¹ Marsh and Murlin: *Am. Jour. Dis. Child.*, 1925, 30, 310.

to Lissauer's surface formula. This was 10 per cent lower than the figures obtained by Murlin in the case of normal babies born at term. Several interesting points were brought out by Marsh and Murlin. They found the metabolism lowest on the seventh day. The respiratory quotients were very low, averaging 0.74 up to the fifth day of life and then 0.79 for three days more. The muscular exertion of crying doubled the metabolism and the heat production can be

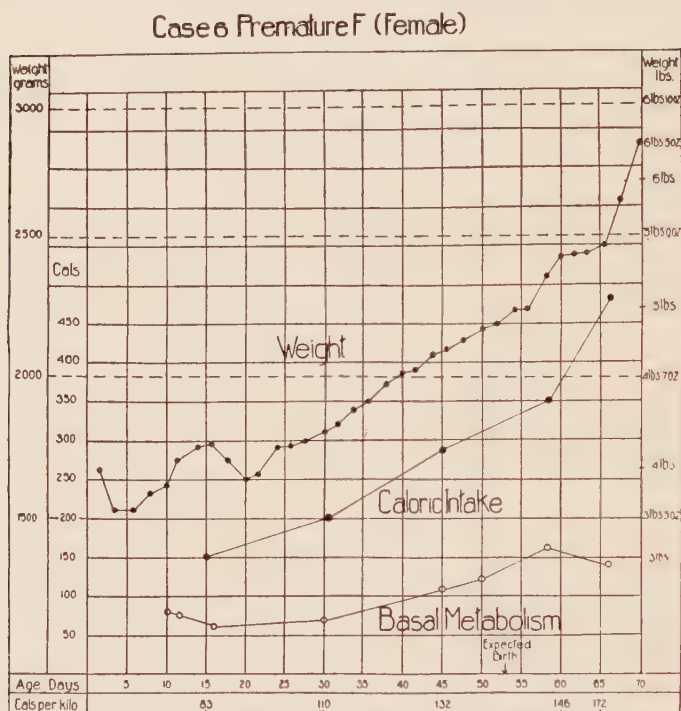


FIG. 22.—Premature F. (female). (Talbot.)

roughly estimated by remembering that crying for 1 per cent of the time increases the metabolism 1 per cent. There were some indications of a considerable increase in the heat production after large portions of food but quantitative tests were impossible.

There are many excellent studies of the metabolism of the new-born. They are well reviewed by Benedict and Talbot¹

¹ Benedict and Talbot: Carnegie Institution of Washington Publication No. 233, 1915.

and by Murlin.¹ The former have performed the useful service of translating from the Danish the classical work of Hasselbalch,² which was for years unavailable for most of the workers in this field. Hasselbalch demonstrated that the basal metabolism of the new-born per kilogram is hardly greater than that of the adult. This means that, according to surface area, it is lower than that of the adult and much lower than that of older infants and children. He found also that the respiratory quotient is very high, indicating that the infant is metabolizing stored glycogen during the first few hours of life. One baby cried for two-thirds of one experiment, and its metabolism was double that found in a period when it was asleep.

This work was not known in America when Benedict and Talbot³ and independently Bailey and Murlin⁴ published their studies on the metabolism of infants, including the new-born. Bailey and Murlin estimate the basal metabolism of the new-born at 1.7 to 2.0 calories per kilogram, a figure which is above that of the average adult, who produces about 1 calorie per kilogram per hour. According to Meeh's formula for children, the metabolism is 25 calories per square meter per hour, a figure below that for adults. They stated that vigorous crying does not raise the figure more than 40 per cent. While they observed high respiratory quotients at six hours of age, they found that the supply of glycogen was rapidly exhausted and that at the end of twenty-four hours they reached a stage of practically pure protein-fat combustion.

Benedict and Talbot,⁵ in a later publication, found an average basal metabolism 1.7 calories per kilogram per hour and an average of 26.7 calories per square meter per hour, using Lissauer's formula ($10.3 \sqrt[3]{Wt^2}$). According to all standards there was considerable variation, showing, as we might expect, that the regulation of metabolism is not well

¹ Murlin: *Endocrinology and Metabolism*, New York, D. Appleton & Co. 1922, 3, 627.

² Hasselbalch: *Bibliot. f. Læger*, Copenhagen, 1904, 8, 219.

³ Benedict and Talbot: *Carnegie Institution of Washington Publication No.* 201, 1914; *Am. Jour. Dis. Child.*, 1914, 8, 1.

⁴ Bailey and Murlin: *Proc. Soc. Exper. Biol. and Med.*, 1914, 11, 109; *Am. Jour. Obstet.*, 1915, 71, 526.

⁵ Benedict and Talbot: *Carnegie Institution of Washington Publication No.* 233, 1915.

established in the first few days of the new existence. They suggest a formula

$$\text{Length in cm.} \times 12.65 \times 10.3\sqrt[3]{\text{Wt}^2}$$

which gives a somewhat closer prediction of the metabolism than any other.

Metabolism of Older Children.—A few years ago there were not many satisfactory studies of the metabolism of children. The technic is difficult, since it is hard to keep the youngsters quiet. Young children are quiet only when asleep and sleep quietly only if the stomachs are comfortably filled with food. This introduces two factors which make it impossible to fulfill the requirements of basal experiments in adults. The food stimulates the metabolism above its basal level; the sleep may or may not depress metabolism. Nevertheless, many good investigations have been made in the last few years and one who reviews the subject finds his table piled high with monographs and reprints. We cannot here mention them all by name, but refer the reader to the publications of Benedict and Talbot.¹

Magnus-Levy and Falk² discovered the main facts. Later Howland,³ Benedict and Talbot, Murlin and Hoobler,⁴ Du Bois,⁵ Olmstead, Barr and Du Bois,⁶ Bedale⁷ and MacLeod⁸ using approximately the same general technic, have collected a large number of experiments on normal children. Howland, with Lusk's respiration chamber, demonstrated that the direct and indirect methods of calorimetry agree closely in small children, and this was confirmed for older boys in the Sage calorimeter. Murlin and Hoobler clearly pointed out the fact that metabolism per square meter of surface increased during the first few months of life. Benedict and Talbot, in Boston, studied a large number of children and furnished most of the data on which all the modern curves are based.

¹ Benedict and Talbot: Carnegie Institution of Washington Publication No. 201, 1914; Publication No. 302, 1921.

² Magnus-Levy and Falk: Arch. f. Anat. u. Physiol., 1899, Suppl., p. 314.

³ Howland: Ztschr. f. physiol. Chem., 1911, 74, 1.

⁴ Murlin and Hoobler: Am. Jour. Dis. Child., 1915, 9, 81.

⁵ Du Bois: Clin. Cal. 12, Arch. Int. Med., 1916, 17, 887.

⁶ Olmstead, Barr and Du Bois: Clin. Cal. 27, Arch. Int. Med., 1918, 21, 621.

⁷ Bedale: Proc. Roy. Soc. B., 1923, 94, 368.

⁸ MacLeod, Grace: Studies of the Normal Basal Energy Requirement, Dissert. Columbia Univ., New York, 1924.

We must remember, however, that, on account of the necessity of giving food, the figures are somewhat above the basal. They estimate an increase of 8 to 15 per cent, but this may perhaps be considered a little high in the light of some recent work on the specific dynamic action of small meals. Benedict and Talbot^{1,2} have published graphic charts showing their results in individual cases, with smoothed curves indicating the averages. The surface area of the children was determined either by the Lissauer method, as modified by Benedict and Talbot, or by the linear or height-weight formula of the Russell Sage Institute of Pathology.

Talbot³ has published a useful set of charts showing his normal standards for the metabolism of children. He has drawn lines 10 per cent above and 10 per cent below the curve, representing the averages. He states that "the metabolism during puberty will have to be studied further before any standards may be accepted, and the age periods on these charts after twelve years should be taken only as temporary suggestions."

The question of metabolism just prior to and just after puberty has not yet been settled. The older investigators⁴ believed that there was an increase in the prepubescent period, and this was supported by the work of Du Bois,⁵ who studied a group of Boy Scouts before the onset of puberty. This was a sturdy set of boys from a suburb, more athletic than a similar group from the city. In order to keep them from feeling faint they were allowed a small breakfast before making the trip to the city, but work with adults had shown that a similar meal did not increase metabolism appreciably. Each boy was in the calorimeter for two periods of about one hour each, and in one period was allowed to read quietly. On the whole, the boys seemed to be fully as quiet as the adult subjects. The results showed a surprisingly high metabolism, 25 per cent above the adult level. Two years later the same boys were studied by Olmstead, Barr, and Du Bois,⁶ at a time

Talbot: *Physiol. Rev.*, 1925, 5, 477; *Monatschr. f. Kinderheilk.*, 1924, 27, 465.

² Benedict and Talbot: Carnegie Institution of Washington Publication No. 302, 1921.

³ Talbot: *Am. Jour. Dis. Child.*, 1921, 21, 519.

⁴ Andral and Gavarret: *Ann. de chim. et phys.*, 1843, 8, 129. Sondén and Tigerstedt: *Skand. Arch. f. Physiol.*, 1895, 6, 1. Olin: *Finska Läkeresällskapets Handl.*, Helsingfors, 1915, 57, 1434.

⁵ Du Bois: *Clin. Cal.* 12, *Arch. Int. Med.*, 1916, 17, 887.

⁶ Olmstead, Barr and Du Bois: *Clin. Cal.* 27, *Arch. Int. Med.*, 1918, 21, 621.

when there were signs of puberty in all the boys and it was found that their metabolism had fallen until it was only 11 per cent above that of adults according to surface area.

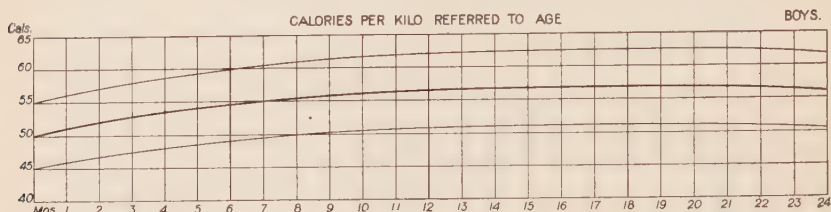


FIG. 23.—Basal metabolism of boys, calories per kilogram of body weight per twenty-four hours during the first twenty-four months of age. (Talbot.)

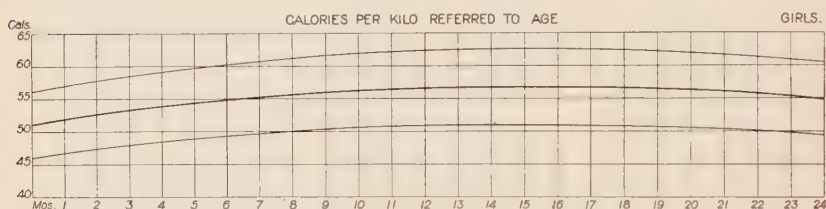


FIG. 24.—Basal metabolism of girls, calories per kilogram of body weight per twenty-four hours during the first twenty-four months of age. (Talbot.)

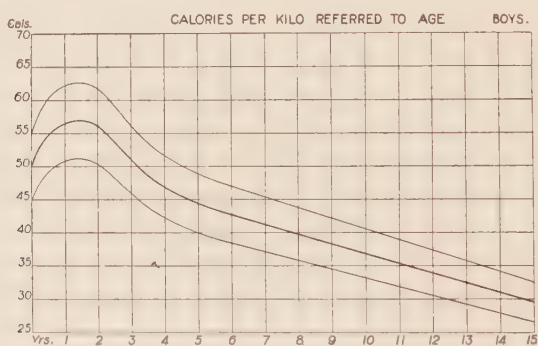


FIG. 25.—Basal metabolism, calories per kilogram of body weight for twenty-four hours of boys at different ages. The curve is projected from twelve years upward. (Talbot.)

Murlin justly points out that there are not enough basal experiments in the literature of boys just before and just after this period to warrant the inference of a distinct rise in

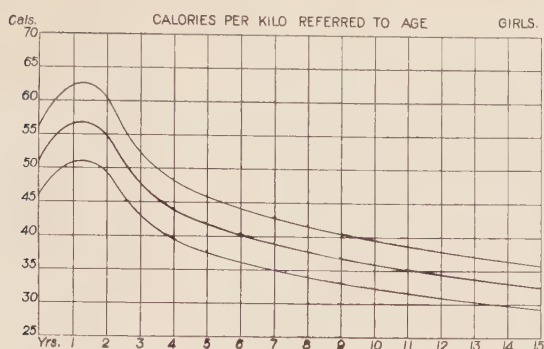


FIG. 26.—Basal metabolism, calories per kilogram of body weight for twenty-four hours of girls at different ages. The curve is projected from twelve years upward. (Talbot.)

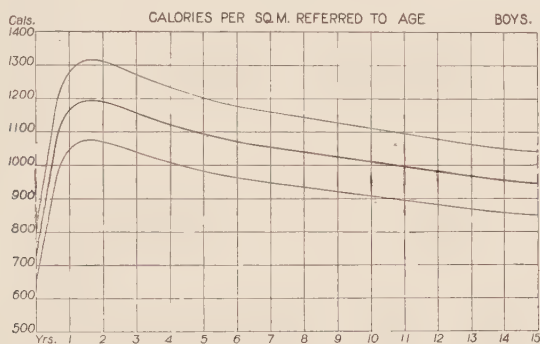


FIG. 27.—Basal metabolism, calories per square meter of body surface for twenty-four hours of boys at different ages. The curve is projected from twelve years upward. (Talbot.)

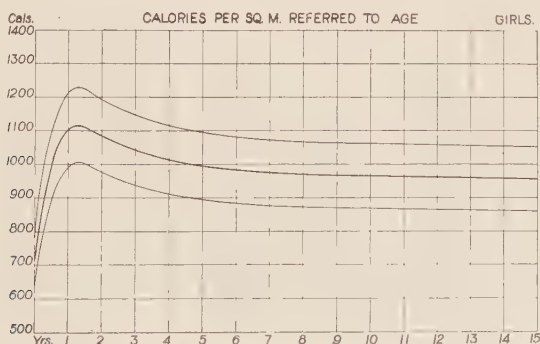


FIG. 28.—Basal metabolism, calories per square meter of body surface for twenty-four hours of girls at different ages. The curve is projected from twelve years upward. (Talbot.)

metabolism in the prepubescent age above that of adjacent ages. Benedict and Talbot, in a few observations at this period of life, find no such increase, but they admit that their experiments are not yet sufficient to warrant a definite conclusion. In one of their girls, whose metabolism was measured before and after the onset of puberty, there was a distinct rise in metabolism in the second observation.

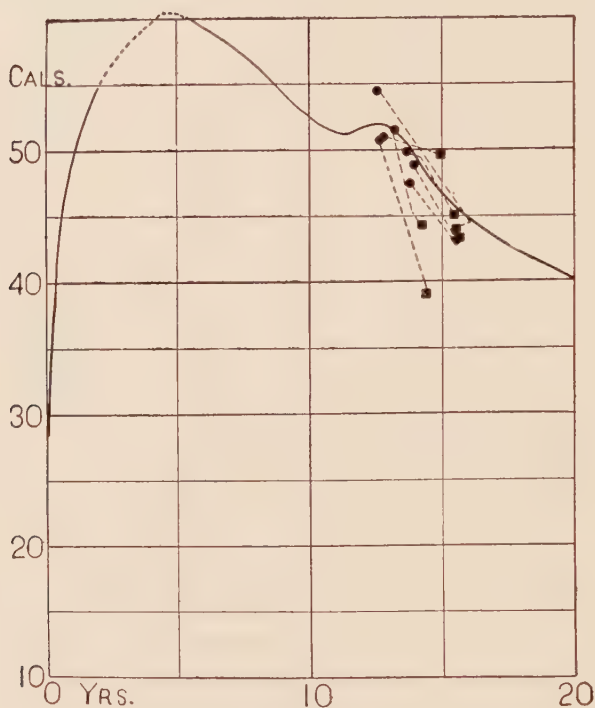


FIG. 29.—Basal metabolism of Boy Scouts in 1915 and 1917.

Benedict and Talbot have very properly called attention to the large variations between the figures for the indirect calorimetry for the two consecutive periods of one hour each. It has been the custom of the Sage laboratory to average two basal hours, since longer periods usually give smaller technical errors. Benedict believes that this is legitimate if the differences are 3 to 4 per cent, but that greater variations indicate muscular activity in the higher of the two periods. The results are shown in Fig. 29.

Benedict and Hendry¹ have studied the energy requirements of girls from twelve to seventeen years of age, using an experimental procedure which was quite different from that previously applied to the study of children. They gathered 9 groups of Girl Scouts, each consisting of 11 or 12 individuals of about the same age but naturally showing considerable variations with regard to puberty. The girls were given supper at 6 P.M. At 10.30 they entered a large, well-ventilated respiration chamber where they slept comfortably until morning. The minimal carbon dioxide production was secured some time between 1.30 and 5 A.M. and the calories were calculated from a respiratory quotient obtained by stopping the ventilation for an hour and analyzing the air.

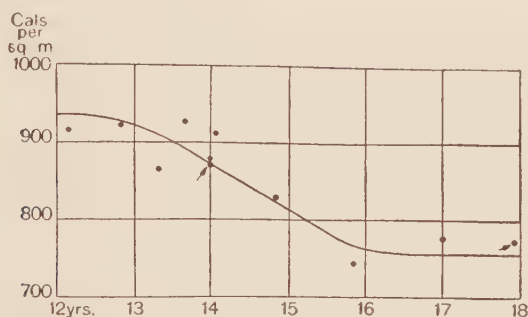


FIG. 30.—Basal heat production of sleeping girls per square meter of body surface per twenty-four hours referred to age. (Benedict and Hendry.)

Benedict and Hendry, using their figures for weights above 38 kilograms and those of Benedict and Talbot for weights below 32 kilograms, have drawn a curve of the calories per square meter referred to weight. They say,

“ . . . There is a hint of a distinct decrease in the metabolism per square meter of body surface immediately following the prepubescent stage, this decrease pursuing a fairly regular course as far as the girls were studied. However, by reference to the earlier charts . . . it can be seen that the distribution of the individual points indicating those girls who had not reached puberty gives very little ground for assuming any special influence of puberty or the prepubertal age upon the metabolism of groups of girls.”

We must remember that these curves can be used only for comparison with other cases studied at the dead of night. It

¹ Benedict and Hendry: Boston Med. and Surg. Jour., 1921, 134, 217, 257, 282, 297, 329.

is difficult to estimate how much the metabolism is depressed under these conditions. Benedict and Hendry give the average carbon dioxide production between 11.30 P.M. and 6.30 A.M. and also the heat production during the period of lowest metabolism. These minimal figures average 5.4 per cent below the average metabolism and in two instances are as much as 10 per cent below the average for the same group.

A remarkably interesting study of the total food requirements of children has been made in Great Britain by Miss E. M. Bedale¹ who examined a large number of boys and girls in a boarding school. Using Douglas bags, she determined the basal metabolism of the children before they left their beds in the early morning and measured the oxygen consumption during their various sports, studies, and other activities. The results obtained on 57 boys have been given in Fig. 32.

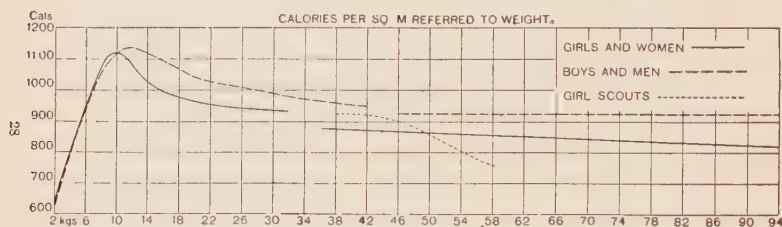


FIG. 31.—Comparison of basal heat production of children and adults per square meter of body surface per twenty-four hours referred to weight. (Benedict and Hendry.)

The curve shows two periods of rising metabolism, one between eight and eleven years and another after fourteen years. The relationship of the changes to the onset of puberty was not determined, and all that we can say is that the heat production of the boys between eight and eighteen years shows wide variations, the figure of 49.5 calories per square meter at eleven years and 38.5 calories at thirteen and a half years differing by 25 per cent. Miss Bedale's figures average about 16 per cent lower than those of the Boy Scouts studied in the Sage calorimeter and are probably closer to the true basal. The American Boy Scouts were brought to the city from a suburb the morning of the observation. The British boys were examined before they got out of bed, and their experimental periods were so short that they could remain motionless.

¹ Bedale, E. M.: Proc. Roy. Soc. (London) B, 1923, 94, 368.

The results obtained by Miss Bedale on 65 girls are given in Fig. 33. It will be noted that there is again the rise in

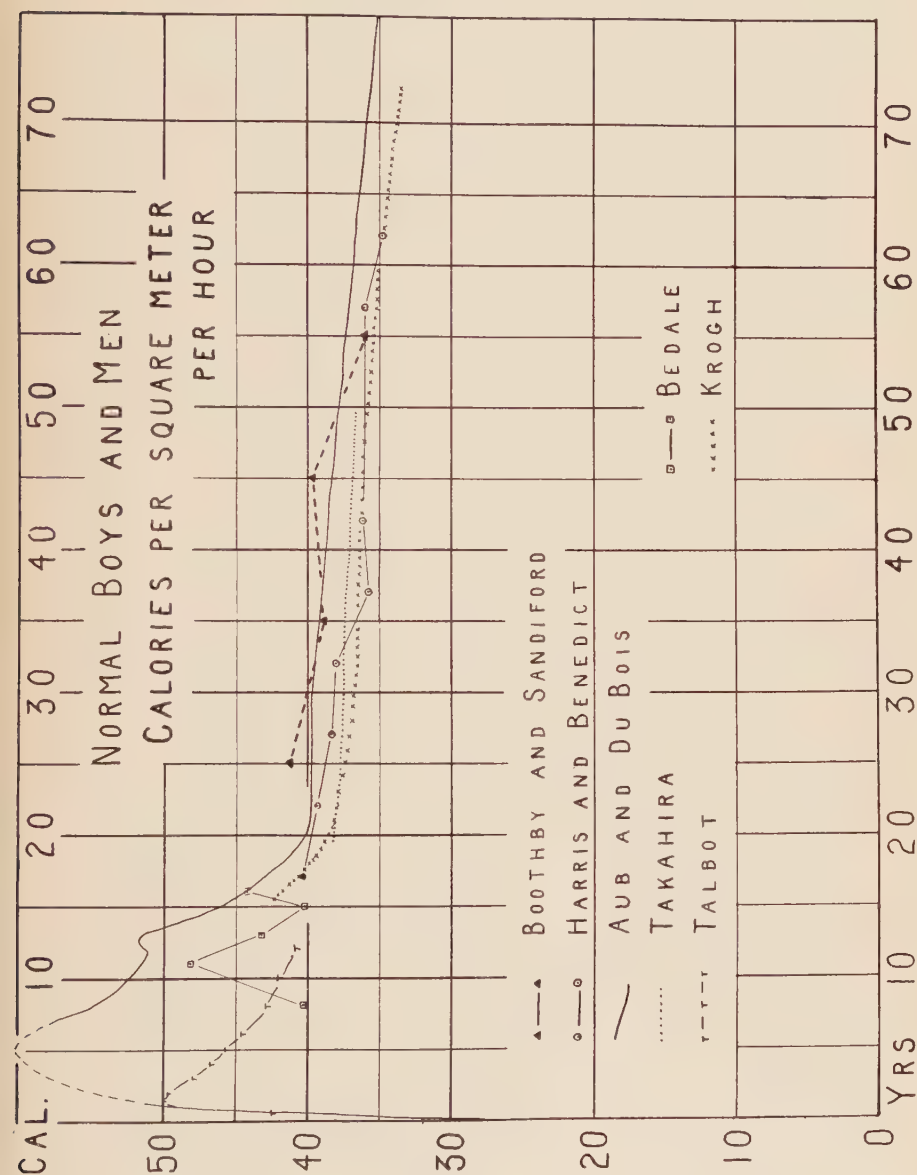


Fig. 32.

heat production just before the age of eleven and a fall after twelve. There was not much difference between the girls

and boys up to the age of eleven, but after twelve years the girls averaged about 9 per cent lower.

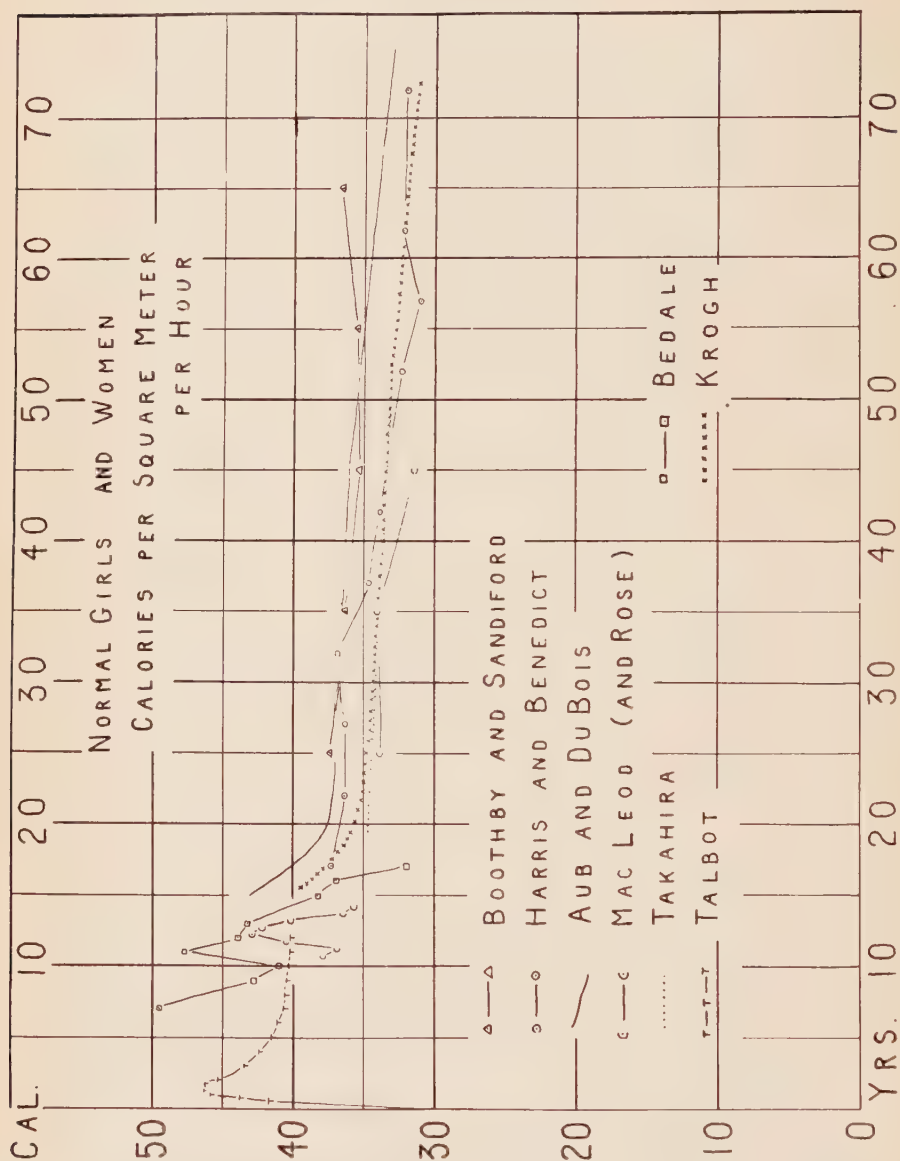


FIG. 33.

These findings have been confirmed on the whole by the extensive studies of Dr. Grace MacLeod¹ who made 362

¹ MacLeod, Grace: Studies of the Normal Basal Energy Requirement, Inaug. Dissert., Columbia Univ., New York, 1924.

basal metabolism tests on 43 different girls attending a day school in New York. The Benedict Portable apparatus was employed, and it was found that the first tests averaged only 2 per cent higher than later tests, proving that there was not much apprehension of the part of the children.

Her results are shown in Fig. 33 and it will be noted that the averages between eleven and fourteen years are only 2 per cent lower than Miss Bedale's. I have recalculated the figures in order to obtain groups six months apart and have plotted them on the chart. This brings out a fall in metabolism at the age of eleven, a short rise to twelve and a half years, and then an abrupt fall. It will be noted that this peak occurs a year earlier in the English girls. This may be due to the fact that the "age of maximum of the adolescent cycle" of growth comes a year earlier in England than in other European countries according to the figures of Brody and Ragsdale.¹ Unfortunately, the averages for America are not given in their tables. On the other hand, the peaks in the curves of Miss Bedale and Miss MacLeod may be fortuitous, and it is possible that we should average the American and English groups, thus obliterating the peaks. Personally I believe that there is a rise in metabolism before puberty, with a subsequent fall, but the proof will come only when a number of individual boys and girls are studied every year, or better every six months, between the ages of ten and sixteen years.

The lesson of all this work is that there are extremely wide variations in the metabolism of normal children between the ages of twelve and sixteen years, just as there are wide variations in the rate of growth and sexual development. This will be discussed in a later chapter.

Talbot² states that there are a number of children with enlargement of the thyroids during puberty and a distinct tendency toward increase in metabolism. He thinks it probable that this increase is due to an overactivity of the thyroid, but points out the need of more data. Janet³ also suggests that there may be a physiological hyperthyroidism at the period before puberty.

¹ Brody, S., and Ragsdale, A. G.: *Jour. Gen. Physiol.*, 1922, 5, 205.

² Talbot, F.: *Monatschr. f. Kinderheilk.*, 1924, 27, 465; *Phys. Rev.*, 1925, 5, 477.

³ Janet: *Jour. méd. Fr.*, 1923, 12, No. 6, June.

Cameron¹ in studying Winnipeg school children obtained curves which were distinctly above the Benedict and Talbot predicted values. There are indications in his work of a drop in metabolism in adolescents. Göttche,² who investigated the specific dynamic actions of proteins in childhood and puberty, noted at the beginning of puberty about one half the children showed a marked increase in the basal metabolism and a diminution in the specific dynamic action. He believes that at this time there is an increased function of the thyroid and he raises the question as to a possible diminution in the function of hypophysis.

Metabolism in Adult Life.—In all the charts given in the previous pages there are clear indications of a progressive

TABLE 19.—ALTERATIONS OF METABOLISM WITH AGE (HARRIS AND BENEDICT)

Age.	Men.				Women.			
	N.	Mean total heat production.	Mean heat per kg.	Mean heat per sq. m.	N.	Mean total heat production.	Mean heat per kg.	Mean heat per sq. m.
15 to 19 = 17	11	1753	26.95	968.4	12	1371	26.51	894.8
20 to 24 = 22	59	1676	26.10	946.2	35	1371	25.16	870.6
25 to 29 = 27	33	1590	25.90	919.6	20	1335	25.83	868.5
30 to 34 = 32	15	1624	25.59	913.1	4	1404	24.25	881.3
35 to 39 = 37	7	1520	23.00	857.0	9	1322	24.32	828.3
40 to 44 = 42	5	1511	24.58	867.8	6	1427	21.35	809.7
45 to 49 = 47	1	1365	22.20	771.0	1	1608	26.80	975.0
50 to 54 = 52	6	1269	21.12	772.2
55 to 59 = 57	2	1373	24.70	864.0	4	1290	19.20	741.3
60 to 64 = 62	3	1541	21.47	836.0	3	1238	22.20	768.3
65 to 69 = 67	1	1150	20.60	723.0
70 to 74 = 72	2	1253	21.10	768.0

decrease in metabolism after the peak in early childhood. It will be noted that this peak was sketched in at about three years in the early Sage chart at a time when there was only 1 experiment between the ages of one and six years. Benedict and Talbot have demonstrated that the metabolism is highest between one and two years, but the general shape of the curve has not been changed. The Sage chart indicated a smaller drop between twenty and thirty years of age than at other periods. It is quite possible that the age effect is counteracted by increasing muscular development. Harris and

¹ Cameron: *Canad. Med. Assn. Jour.*, 1925, **15**, 1022.

² Göttsche: *Klin. Wchnschr.*, 1925, **4**, 2062.

Benedict¹ have made a careful statistical study of the effect of age in their series of normals and have concluded that the rate of change throughout the age range of adult life is essentially uniform. In their series, shown in Table 19, there are only 6 men over forty-four years and only 1 woman between forty-five and forty-nine years, and the figures at these ages are therefore not so well established as at other periods.

Several important studies of the normal metabolism have been published since the analysis of Harris and Benedict. Boothby and Sandiford,² who use face masks and a spirometer, have grouped their data on 102 normal persons and have found that they agree rather closely with the Sage standards. Their work is shown in Figs. 32 and 33. They have supplemented their study of the normal controls by comparing them with 455 patients suffering from chronic nervous exhaustion, migraine, and obesity, conditions which are not supposed to alter the metabolism. This group agrees quite closely with the first, as will be seen in Tables 33 and 34.

TABLE 20.—CALORIES PER SQUARE METER OF BODY SURFACE PER HOUR (BAILEY) (DuBois Height-Weight Formula).

Age, years.	Males.	Females.	Age, years.	Males.	Females.
4	56.0	53.0	39	39.0	36.4
5	55.0	52.0	40	38.9	36.3
6	54.0	51.0	41	38.9	36.2
7	53.0	50.0	42	38.8	36.2
8	52.0	49.0	43	38.8	36.1
9	51.0	48.0	44	38.7	36.1
10	50.0	47.0	45	38.6	36.0
11	49.0	46.0	46	38.5	36.0
12	48.0	45.0	47	38.4	35.9
13	47.0	44.0	48	38.4	35.8
14	46.0	43.0	49	38.3	35.7
15	45.0	42.0	50	38.2	35.6
16	44.0	41.0	51	38.2	35.5
17	43.0	40.0	52	38.1	35.4
18	42.0	39.0	53	38.0	35.3
19	41.0	38.0	54	38.0	35.3
20	40.0	37.0	55	38.0	35.2
21 }	39.9	37.0	56	38.0	35.1
30 }			57	37.9	35.0
31	39.8	36.8	58	37.9	35.0
32	39.7	36.7	59	37.8	35.0
33	39.5	36.7	60	37.7	34.9
34	39.3	36.6	61	37.7	34.9
35	39.2	36.5	62	37.6	34.8
36	39.1	36.5	63	37.5	34.8
37	39.1	36.5	64	37.4	34.7
38	39.0	36.4	65	37.3	34.7

¹ Harris and Benedict: Carnegie Institution of Washington Publication No. 279, 1919, p. 241.

² Boothby, W. M., and Sandiford, I.: Jour. Biol. Chem., 1922, 54, 767.

Dr. Cameron V. Bailey of the Post-Graduate Hospital, New York, has had an unusually large experience with the basal metabolism tests, perhaps second only to that of Boothby and Sandiford. His results on "apparently normal *patients* undergoing a general physical examination" are given in the recent edition of Hawk and Bergheim.¹

Bailey employs a modified Tissot spirometer and face mask. His results shown in Table 20 agree on the whole very closely with the so-called Sage (Aub and DuBois) standards. His curves are slightly lower in childhood and slightly higher after the age of fifty years, but practically the same in early adult life. Bailey says "The results are probably not 'basal' but are normal for the standard conditions of the test."

Blunt and Dye² studied 17 university women between the ages of twenty-four and forty-four years, using the Benedict Portable apparatus. Their figures averaged 4.1 per cent below the Harris-Benedict standards and 6.5 per cent below the Aub-Du Bois curve. MacLeod and Rose³ reported 92 normal women between the ages of twenty and fifty years, using also the Benedict Portable. Here again the figures average 4.4 per cent below the Harris-Benedict and 8.6 per cent below the Aub-Du Bois curves.

One of the most comprehensive studies of the normal metabolism has been made by Takahira,⁴ in Tokyo Institute for Nutrition, Professor Tadasu Saiki, Director. One hundred and twenty Japanese men and women of various classes were examined for three or four consecutive half-hour periods in a Benedict cot chamber. The figures will be referred to often, but it is sufficient at the present time to say that the men averaged 37.33 calories per square meter per hour (5.5 per cent below the Aub-Du Bois curve) and the women 33.84 calories per square meter per hour (7.3 per cent below the Aub-Du Bois curve). It is hardly fair to average the Oriental figures with those obtained in America, but the lines representing the changes with age have been added to Figs. 32 and 33.

There are no investigators better acquainted with the funda-

¹ Hawk, P. B., and Bergheim, O.: Practical Physiological Chemistry, 9th ed., P. Blakiston's Son & Co., Philadelphia, 1926, appendix, Table 3, p. 896.

² Blunt, K., and Dye, M.: Jour. Biol. Chem., 1921, **47**, 69.

³ MacLeod, G., and Rose, M. S.: Am. Jour. Physiol., 1925, **72**, 236.

⁴ Takahira: Report of the Metabolic Laboratory, The Imperial Government Institute for Nutrition, Tokyo, Japan, 1925, **1**, No. 1.

mental principles of basal metabolism and their clinical applications than Drs. August and Marie Krogh, of Copenhagen. I have not been able to find their compilation of normal controls, but give great weight to August Krogh's statement in 1923:

"The Du Bois method and table for computing the basal metabolism give results which are on the average too high (about 4 per cent or more)"

In some tables published in 1925 for use with the Krogh respiration apparatus¹ there are given the Harris-Benedict normal values and also "figures calculated from Du Bois' determinations, but with a 6 per cent reduction, corresponding to the more rigorous definition of standard conditions imposed." Those curves are also represented in Figs. 32 and 33.

It is interesting to note that F. G. Benedict also believes that the older estimates of the heat production of women were too high. Writing on the metabolism of Oriental women with MacLeod and Crofts,² he says:

"An examination of data obtained in our several laboratories (but not here published) and data published elsewhere on normal women leads us to the belief that the present standards for American women are too high, indeed, approximately 5 per cent too high."

Therefore if we glance at Fig. 32, which shows the metabolism of men expressed in terms of calories per square meter per hour, we note between the ages of twenty and forty years a slight fall of the heat production. The curves of Harris and Benedict and Boothby and Sandiford show a slight rise after the age of forty years but the number of subjects above this age was not large in either series. In Fig. 33 which gives the same curves for women the Harris-Benedict curve is almost level between the ages of twenty-two and thirty-two years, the Boothby and Sandiford curve almost level between thirty-five and sixty-five years and the Blunt and Dye curve almost level between twenty and forty-four years. On the whole, one gains the picture of a gradual fall between the ages of twenty-two and sixty years at about the same rate as the fall in the men.

¹ Krogh, A.: *Boston Med. and Surg. Jour.*, 1923, **189**, 313; *Krogh's Recording Respiration Apparatus. Tables of Normal Metabolic Rates after Du Bois and Benedict-Harris*, J. H. Schultz, Copenhagen, 1925.

² MacLeod, G., Crofts, E. E., and Benedict, F. G.: *Am. Jour. Physiol.*, 1925, **73**, 449.

Unfortunately, we have not a large number of experiments on old people. Magnus-Levy and Falk found that the metabolism was low in old age, and the original Sage curve was based on their work. Later Aub and Du Bois¹ studied 6 old men from the New York City Home for Aged and Infirm. The results are given in Table 21. One old man Charles W.

TABLE 21.—OLD MEN. SUMMARY.

Case No. and name.	Age, yrs.	Weight, kg.	Height, cm.	Signs of senility.	Surface area (ln.), sq. m.	Total calories in two hours.		Calories per hour.		Per cent from adult, av. 39.7.	Av. R. Q.	Av. pulse.
						In- direct.	Direct.	Per kg.	Per sq. m.			
1. A. O'C.	77	69.7	171	+	1.87	133.3	143.4	0.962	35.6	-10	0.81	59
2. H. L.	78	67.9	167	++	1.85	154.0	150.5	1.130	(41.6) ¹	(+5) ¹	0.78	68
.. H. L.	..	68.9	1.85	130.7	126.1	0.949	35.3	-11	0.86	71
3. C. H.	79	52.9	163	+	1.66	118.0	114.6	1.120	35.6	-10	0.80	73
4. C. W.	80	69.1	164	+++	1.82	101.7	105.3	0.736	27.9 ²	-30 ²	0.82	55
5. W. C.	83	62.9	163	++	1.73	118.8	121.2	0.944	34.3	-14	0.86	65
6. J. B.	83	50.5	158	+++	1.48	103.3	98.2	1.020	34.9	-12	0.77	50
Total or average	859.8	859.3	..	35.1	..	0.81	

¹ Excluded from averages on account of restlessness.

² Excluded from averages on account of unusually low metabolism.

showed a metabolism 21 per cent below the mean of this group and he was excluded from the averages. Harris and Benedict² criticize this procedure, and there is much to be said on their side. They also feel that the case histories show that these old men must have been rather unusual physically to have survived their previous habits of life. The average results are only slightly higher than those of Magnus-Levy and Falk but considerably higher than the line indicated by the younger men of Harris and Benedict, who had no male subjects over sixty-three years of age. Extrapolation is somewhat hazardous, and it does not necessarily follow that metabolism will continue to decrease at the same rate between the ages of forty and sixty years and between the ages of sixty and eighty years.

¹ Aub and Du Bois: Clin. Cal. 19, Arch. Int. Med., 1917, 19, 823.

² Harris and Benedict: Carnegie Institution of Washington Publication No. 279, 1919.

Krogh¹ believes that the Sage method of introducing the age factor is in much better agreement with biological principles than the Harris-Benedict formula.

Influence of Sex.—Sondén and Tigerstedt² found that the carbon dioxide excretion of boys was greater than that of girls. Magnus-Levy and Falk³ called attention to the fact that metabolism of women was 5 per cent lower than that of men in youth and in old age. They did not believe that there was any difference in the prime of life, and this seems to be almost the only point in which the magnificent work of Magnus-Levy has not been substantiated by subsequent investigators. In 1915 Benedict and Emmes⁴ made a careful comparison of two large groups of men and women and estimated that the latter averaged 5 or 6 per cent lower.

Gephart and Du Bois⁵ applied the new height-weight surface area formula to the averages of the 68 women given by Benedict and Emmes and to the 7 women studied by Means and obtained an average 7 per cent below that of men. Harris and Benedict⁶ have made an elaborate statistical study of this subject, using 39 different methods of comparison. They say, "The general average percentage deficiency when weight and stature only are considered in the calculations of the theoretical heat productions is 7.3 per cent. When age is taken into account as well as stature and body weight, the deficiency is 6.2 per cent." Using their multiple prediction formula for men on the series of women, they find that when the individuals are classified by age, the theoretical and the empirical heat productions are separated by roughly the same distance throughout the whole age range. Takahira found the metabolism of Japanese men averaged 37.33 calories per square meter per hour and the women of about the same age distribution 33.84 calories, a figure 9.3 per cent below that of the men. It is quite possible that the sex difference is greater in Orientals. I am inclined to believe that differences in occupation, athletic training etc. are important matters which have been more or less neglected

¹ Krogh: Boston Med. and Surg. Jour., 1923, 189, 313.

² Sondén and Tigerstedt: Skand. Arch. f. Physiol., 1895, 6, 1.

³ Magnus-Levy and Falk: Arch. f. Anat. u. Physiol., 1899, Suppl., p. 314.

⁴ Benedict and Emmes: Jour. Biol. Chem., 1915, 20, 253.

⁵ Gephart and Du Bois: Clin. Cal. 13, Arch. Int. Med., 1916, 17, 902.

⁶ Harris and Benedict: Carnegie Institution of Washington Publication No. 279, 1919.

by all observers except Takahira and that it is difficult to determine the exact extent of the sex factor.

Benedict and Talbot¹ find no sensible difference between the heat productions of the two sexes in the first week of life. In their 1921 publication they give a series of charts showing the average metabolism of boys and girls. Speaking of these charts, they say, "We have clear evidence of a sexual differentiation in basal metabolism exhibited above 11 kilograms and after this the boys show persistently a somewhat higher metabolism than girls of the same weight. . . . After a weight of about 14 kilograms the differences between the two sexes remain almost uniformly constant throughout the entire weight ranges." On the other hand Bedale² who studied vigorous boys and girls in the same boarding school found but little difference in the basal metabolism of the two sexes at the ages of twelve and thirteen years. This might be due to differences in the changes of metabolism before the onset of puberty.

Harris and Benedict found the largest divergence between the theoretical and the actual heat productions when the theoretical values for women are computed by assuming that the heat production of a woman should be the same as that of a man of like weight. Magnus-Levy and Falk had pointed out that women have a larger proportion of body fat than men. The divergence may be the result of the gonads, but this would hardly explain the sex difference at the tender age of three years. Muscular development would not explain matters either, since little girls can usually hold their own with boys of the same size in the competitions of childhood. The subject will be discussed again in another chapter.

Influence of Air, Temperature, Climate, Athletic Training.— In cold-blooded animals the body temperature is dependent on that of the surrounding medium. It is not surprising, therefore, that the metabolism increases rapidly when the temperature of the air or water in which they live is increased up to a certain point. This subject has been discussed in a most interesting manner by Krogh³ who has expressed some

¹ Benedict and Talbot: Carnegie Institution of Washington Publication No. 233, 1915. Harris and Benedict: Carnegie Institution of Washington Publication No. 279, 1919, p. 219.

² Bedale: Proc. Roy. Soc. B., 1923, 94, 368.

³ Krogh: The Respiratory Exchange of Animals and Man, London, Longmans, Green & Co., 1916, p. 84.

of the findings in a chart. Similar curves are found on pithed rabbits and Krogh has included the data obtained on a curarized young dog in the same figure. The effect of temperature on warm-blooded animals has been treated in detail by Lusk¹ who has clarified the somewhat difficult theories of Rubner regarding heat regulation. The German investigator had found that a guinea-pig showed an increased metabolism when exposed to environmental temperatures below 30° C. Since there was no apparent increase in muscular activity to account for the very high metabolism at 0° C. and 11° C., Rubner believed that there was a "chemical regulation" of temperature. Animals protected by thick fur or a heavy layer of subcutaneous fat do not show much change in metabolism with changes in environmental temperature between 20 and 30° C. This, Rubner calls the zone of "physical regulation." With high temperatures the regulation by evaporation, radiation and conduction may become insufficient, particularly in humid air and there may be hyperthermia of the body cells and a consequent rise in metabolism.

Some of the older work by Voit and Rubner indicates a similar mechanism in man. Loewy,² however, believes that in the human subject the increase at low environmental temperature is due entirely to muscular activity, conscious or unconscious shivering. He exposed a series of men to cold air and cold baths and found the metabolism unchanged in 36 per cent and lowered in 16 per cent. In 47 per cent of the subjects it was increased 5 to 91 per cent, but in one-half of these there was visible shivering.

Lefevre³ has for a long time insisted that the true basal metabolism is found only when the subject is immersed in a "neutral bath" at a temperature of 35° to 36° C. though his figures are by no means convincing. F. G. and C. G. Benedict⁴ have reviewed this thoroughly and have arrived at very different conclusions. They studied 1 woman, an artist's model, and 3 men first lightly clothed in a cool room at 16° C. and then in baths at 36° C. The warm bath caused no change in the metabolism of the model but there was a distinct rise in the heat production of the men. Delcourt-Bernard and

¹ Lusk: *Science of Nutrition*, 3d edition, Philadelphia and London, W. B. Saunders Company, 1917, p. 134.

² Loewy, A.: *Arch. f. d. ges. Physiol.*, 1890, **46**, 189.

³ Lefevre: *Bull. Soc. Sci. d. Hyg. Alimen.*, 1922, **10**, 595.

⁴ Benedict, F. G., and Benedict, C. G.: *Ibid*, 1924, **12**, Nos. 8 and 9.

Mayer¹ substantiated this rise but noticed after the bath a fall below the original basal level. Durig and Grau² by means of diathermy administered 4.1-4.8 calories per minute to 3 men whose heat production averaged about 1.2 calories per minute causing a moderate rise in body temperature and profuse sweating but only a slight increase in metabolism which might be expected from the change in body temperature. C. G. and F. G. Benedict and E. F. Du Bois³ studied 3 men and 2 women first at room temperature and then in an oilcloth bag through which was driven a blast of very hot, dry air. The metabolism increased only 5 to 10 per cent and 1 subject gave a maximal increase of 7 per cent in spite of the fact that the air entered the bag at 94° C. and made his feet and legs almost unbearably hot.

Man's skin is moist and from a thermic standpoint man resembles a wet bulb thermometer rather than a dry one. Bearing this in mind McConnell, Yagloglou and Fulton⁴ have exposed a number of men to various levels of the "effective temperatures," an index which takes care of external temperature, humidity and air movement. The results are shown in Fig. 34 and it will be noted that metabolism was lowest at effective temperatures between 75° and 83° F. At higher temperatures there was a rise in rectal temperature, a rise in the respiratory quotient and marked increase in heat production.

Gessler and his associates⁵ studied the response of normal controls and patients when the body was uncovered in a cool room. As a rule the basal metabolism increased 10 to 20 per cent when all clothing was removed. The mechanism of heat regulation has been studied by Barbour and his associates⁶ and they have found that when dogs are exposed to cold, the water is withdrawn from the blood and stored in the skin and subcutaneous tissues. Barbour says: "The 'suit of clothes' (see page 385) which protects those regions

¹ Delcourt-Bernard and Mayer: *Compt. Rend. Soc. de Biol.*, 1925, **92**, 62.

² Durig and Grau: *Biochem. Ztschr.*, 1913, **48**, 480.

³ Benedict, C. G., Benedict, F. G., and Du Bois, E. F.: *Am. Jour. Physiol.*, 1925, **73**, 429.

⁴ McConnell, Yagloglou and Fulton: *U. S. Pub. Health Rep.*, December 5, 1924, **39**, 3075 (Reprint No. 977).

⁵ Gessler: *Pflüger's Arch.*, 1925, **207**, 370, 376, 390, 396, 624; *Deutsch. Arch. f. klin. Med.*, 1925, **148**, 129, 140.

⁶ Barbour: *Am. Jour. Physiol.*, 1925, **73**, 315, 321, 665, **74**, 204, 223.

in which blood now actively circulates is thus further padded by water."

The question of chemical regulation in man is, therefore, still unsettled and we may hope for more work on this subject. As a matter of fact, man adapts himself to cold tempera-

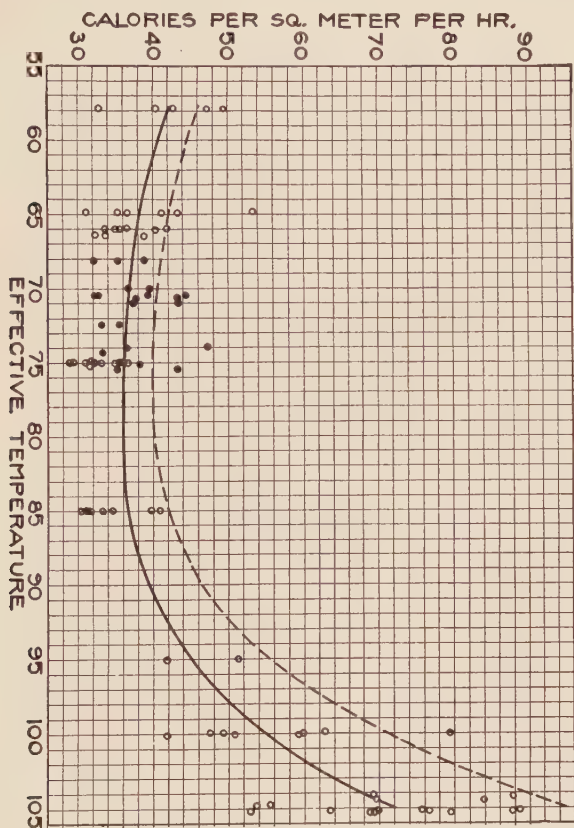


FIG. 34.—Chart showing the results obtained by McConnell, Yagloglou and Fulton on men exposed one to two hours in a chamber with various atmospheric conditions.

tures by warming his houses and increasing his clothing, so there is not much difference in the air surrounding his skin in winter and summer. We have already told how Benedict has shown that there is no appreciable seasonal change in metabolism.

Lindhard¹ who studied his own metabolism in Greenland

¹ Lindhard: Skand. Arch. f. Physiol., 1912, 26, 221.

found a higher level during the period of long Arctic days than during the winter. He ascribes this to the effect of light. Leonard Hill¹ found that the metabolism was much higher sitting outdoors, especially in windy or cold, bracing weather. Hill, Campbell and Gauvain² studied the metabolism of children undergoing open-air treatment, heliotherapy and balneotherapy and noted that all of these increased metabolism. Under the influence of fresh air and sunlight the basal figures were found to be 40 per cent above the Benedict and Talbot standards. Their metabolism in winter was 20 to 30 per cent higher than in summer. They found the rise caused by heliotherapy small compared to that caused by open air. The writers realized that it was perhaps not fair to compare the underweight children in England with the children studied in the Boston respiration chambers. Hafkesbring and Collett³ in a long study of the metabolism of two normal women found the basal figures about 5 per cent higher in cold than in warm weather. Mason and Mason⁴ have noticed a fall in the metabolism of some individuals exposed ultra-violet rays. Fries⁵ on the other hand found no change except in one child whose heat production dropped 24 per cent.

Otto Kestner,⁶ Häberlin,⁷ and their associates find transient rise in metabolism after sunlight or ultra-violet irradiation. In 14 Hamburg children studied before and after a two-months outing at the seashore there was no change in metabolism.

Durig and Zuntz⁸ observed no change in their metabolism during a sea voyage to Teneriffe, but this was a comparatively short affair and did not prove very much. When they reached Teneriffe they ascended the mountain and measured their metabolism at 2160 and 3260 meters altitude. Their work shows practically no change in metabolism at high altitude and this is in accord with the previous work of Zuntz⁹ and his collaborators and of the Anglo-American expedition

¹ Hill: Great Britain Local Government Board Reports, 1914, n. s., No. 100; The Science of Ventilation and Open-air Treatment, vol. 1, Med. Research Council, 1919.

² Hill, Campbell and Gauvain: Brit. Med. Jour., 1922, i, 301.

³ Hafkesbring and Collett: Am. Jour. Physiol., 1924, 70, 73.

⁴ Mason, E. H., and Mason, H.: Arch. Int. Med., in press.

⁵ Fries, M. E.: Proc. Soc. Exper. Biol. and Med., 1925, 22, 431.

⁶ Kestner, Peemöller and Plaut: Klin. Therap. Wchnschr., 1923, 2, 2018.

⁷ Häberlin, Kestner, Lehmann, Wilbrand and Georges: Klin. Wchnschr., 1923, 2, 2020.

⁸ Durig and Zuntz: Biochem. Ztschr., 1912, 39, 422, 435.

⁹ Zuntz: Arch. f. d. ges. Physiol., 1896, 63, 461.

to Pike's Peak.¹ This subject is thoroughly reviewed by Lusk.² Lavoisier and Seguin³ found that breathing pure oxygen did not change the vital processes. This has been confirmed by many other investigators. Benedict and Higgins⁴ have made a large number of experiments on subjects breathing oxygen-rich mixtures up to 90 per cent of this gas and have found no change in the metabolism. Schneider, Truesdell and Clarke⁵ in a careful study of the effects of reducing the barometric pressure in a low pressure chamber noted a reduction of 4.5 to 26 per cent in the metabolism of three-quarters of their subjects. The men were exposed to pressures of 410 to 310 mm. for thirty to sixty minutes. In some prolonged exposures of three and five-tenths to eight hours at 400 mm. the metabolism fell at first and then rose to or above normal, the rise being usually associated with the onset of symptoms of mountain sickness.

Influence of Race.—We know rather little about the differences in the metabolism of the different races. As a matter of fact, almost all of the determinations that we have used have been made in America or Germany. There has been no indication of any difference in the metabolism of these two nationalities or any difference between different parts of the United States. Eijkmann,⁶ working in far-off Batavia, could find no significant change in the basal metabolism. Using a Zuntz-Geppert apparatus he studied 12 Malay servants accustomed to light work, 11 Europeans living in Batavia, rather heavier than the Malays, and compared these with the normal men studied in Germany by Geppert, Loewy and Magnus-Levy. The results are shown in Table 22.

TABLE 22.—COMPARISON OF METABOLISM IN GERMANY AND IN TROPICS.

	Av. weight.	Cc O ₂ per min.	O ₂ calculated for 64 kg.	R. Q.	Cal. per sq. m. per hr.
11 Normal men in Germany	62.0	250.3	250.3	0.775
12 Malays in Batavia	50.4	214.0	251.5	0.882	39.90
11 Europeans living in Batavia	68.0	253.1	245.7	0.791	40.08

¹ Douglas, Haldane, Henderson and Schneider: Trans. Roy. Soc., 1912, 203, 185.

² Lusk: Science of Nutrition, 3d edition, Philadelphia and London, W. B. Saunders Company, 1917, p. 418.

³ Lavoisier and Seguin: Mémoires de l'Acad. des Sci., 1789, p. 185.

⁴ Benedict and Higgins: Am. Jour. Physiol., 1911, 28, 1.

⁵ Schneider, Truesdell and Clarke: Am. Jour. Physiol., 1924, 70, 283; Ibid., 1925, 74, 334.

⁶ Eijkmann: Arch. f. d. ges. Physiol., 1896, 64, 57; Jour. de Physiol. et de Path. Gen., 1921, 19, 33.

A remarkable piece of work has been done in Brazil by A. Ozorio de Almeida¹ who studied the basal metabolism of 10 white men and an equal number of negro laborers using a Tissot gasometer. The white subjects showed an average metabolism 24 per cent lower than the generally accepted standards for the United States. That of the negro laborers was 8 per cent higher than the whites but still much below the figures obtained in the temperate zone. He has recently added a second series of 8 normal white men obtaining an average figure of 33.2 calories per square meter per hour, 16.2 per cent below the Sage standards, 13.6 below those of Harris and Benedict.

This is so unexpected that one naturally searches the article for evidence of some error in technic but none is apparent. The white men were twenty-three to forty years of age, all were born in tropical Brazil and all lived in Rio de Janeiro, 22° 54' S. where the average temperature is 23.4° C. Most of the subjects were doctors who lived a rather sedentary life since exercise is not popular in such hot climates. One young man whose metabolism was 22.7 calories per square meter per hour began to lead a life of great physical activity in order to see if his metabolism would change. In a year it had risen to 32 calories. Ozorio de Almeida has developed an interesting theory to account for his findings. He believes that in sufficient time all the factors which modify the total metabolism will finally alter the value of the basal metabolism. The basal metabolism, therefore, depends on all the factors which in passing have modified the intensity of the habitual metabolism. Among these are muscular work, the level of food intake and the difference between the temperature of the body and the temperature of the air multiplied by the surface area. In the tropics all of these are lower than in the temperate zone.

This theory is quite fascinating. It would account for the increased metabolism of athletes on account of previous muscular work and of children on account of activity and large food intake. It would explain the low metabolism of undernutrition.

The experimental findings of Ozorio de Almeida on which these assumptions are based have not been substantiated by

¹ de Almeida: *Jour. de Physiol. et de Path. Generale*, 1920, 18, 712, 958; 1924, 22, 1248.

many other observers. It is true that Montoro¹ has found in Havana figures which correspond. His average for 10 men was 33.5 calories per square meter per hour with an average 15.5 per cent below the Sage standards and 15.8 per cent below the Harris-Benedict figures. The limits were -8.1 and -31.7 . The average for 5 normal women was 31.9 calories, 13 per cent below both standards, the limits being $+0.5$ and -19.0 . No others seem to have obtained such low figures. Knipping² measured the heat production of 11 Europeans, Malays and Chinese who had lived for a long time in the tropics and obtained an average 6.3 per cent below the Benedict standards. He also found that when Europeans moved to the tropics the metabolism remained constant or rose for a short time and then fell below its original level. Fleming³ has confirmed this report. His average for 20 Americans in America using the Boothby and Sandiford technic with due consideration of the urinary nitrogen was 2.4 per cent below the Sage(?) standards. In the Philippines with exactly the same technic the average of 9 surgical convalescent natives was -8.3 per cent while 12 beriberi patients gave almost exactly the same figure. He also noted that one American whose metabolism was 3 per cent below the standard on arrival in the Philippines showed a fall to -7 per cent after thirteen months residence in the islands.

Takahira's⁴ report on the metabolism of 120 Japanese men and women is of great importance. As we have said before his average for men was 5.5 per cent below the Sage standards while the women were 7.3 below. There were, however, considerable differences between the various groups of Japanese according to their occupations and muscular development and for a strict comparison we should perhaps compare each group with similar Americans but the figures for this are not available. Takahira did not believe that there was any significant difference between the two races and we must certainly agree with him if we accept Krogh's reduction of 6 per cent in the Sage standards.

On the other hand a significant publication in this country

¹ Montoro: *San mil. Habana*, 1921-1922, **1**, 255.

² Knipping: *Arch. f. Schiff. u. Trop. Hyg.*, 1923, **27**, 169.

³ Fleming, W. D.: *Jour. Met. Res.*, 1923, **4**, 105; *Am. Jour. Trop. Med.*, 1925, **5**, 283.

⁴ Takahira: *Report of the Metabolic Laboratory, The Imp. Govt. Inst. for Nutrition, Tokyo*, 1925, vol. **1**, No. **1**.

indicates a lowered metabolism of Oriental women. MacLeod, Crofts and Benedict¹ have studied 7 Chinese and 2 Japanese women who had been students in American colleges for at least fifteen months, exposed to a New York or New England climate, dietary and general strenuousness of life. Their metabolism averaged 10.4 per cent below the Harris-Benedict standards for women and 10.2 per cent below the Sage standards. The authors have found both of these standards about 5 per cent too high for American college women but this still leaves the Orientals 5 per cent below their colleagues in spite of the fact that the environment has been exactly the same for over a year.

Mukerjee² in a brief note reports that the basal metabolism of fifteen Bengalese students in a medical college in Calcutta averaged "9 per cent lower than generally accepted standards."

In general we may conclude that the Chinese and Japanese show a slightly lower metabolism than Americans or Europeans. White men going to the tropics exhibit a gradual decrease in heat production. There is evidence to indicate that there may be a rather large decrease in the inhabitants of some tropical countries.

The Influence of Diet.—Benedict and Roth found no significant difference in the respiratory metabolism of vegetarians and non-vegetarians and this was confirmed by the calculations of Harris and Benedict.³ Krogh and Lindhard,^{4,5} however, believe that the metabolism is distinctly lower if the previous diet has been low in protein. One of their normal controls had a gradual fall of 20 per cent in this heat production as he continued on a low-protein diet. They also conclude that the basal metabolic rate is lowest when the respiratory quotient is between 0.8 and 0.9. Therefore Krogh in his strict procedure for obtaining the low basal of his new standards requires that for one or two days before the test the diet shall contain as little protein as possible and that it shall consist largely of carbohydrates in order that the quotient may be somewhere between 0.8 and 0.9 in the morn-

¹ MacLeod, Crofts and Benedict: *Am. Jour. Physiol.*, 1925, **73**, 449.

² Mukerjee: *Jour. Am. Med. Assn.*, 1926, **86**, 1384.

³ Harris and Benedict: *Carnegie Institution of Washington, Pub. No. 279*, 1919, p. 246.

⁴ Krogh and Lindhard: *Biochem. Jour.*, 1920, **14**, 290.

⁵ Krogh, A.: *Wien. klin. Wchnschr.*, 1922, **35**, 290; *Boston Med. and Surg. Jour.*, 1923, **189**, 313.

ing twelve to fourteen hours after the last meal. In his German article he gives a sample diet but some of the dishes such as beer soup are not obtainable in this country.

Athletic Training.—Benedict and Smith¹ found that the basal metabolism of trained athletes averaged 6 to 7 per cent higher than that of non-athletic men. Gephart and Du Bois² recalculated these according to age and found that they were only 2.5 per cent higher than the Sage standards which were based on data including these very athletes. Harris and Benedict, in 1919, compared the athletes with their multiple prediction formula and estimated an average increase of 3.03 per cent. This may indicate that metabolism is proportional to protoplasmic mass or it may be a reflection of the higher nutritive plane demanded by those who engage in athletics.

Takahira has divided his Japanese normal controls into groups according to their occupations and compared their metabolism averaging their divergences from the Sage, Harris-Benedict and Dreyer standards as shown in Table 23. It will be noted that there is a difference of about 13 per cent between the highest and lowest groups of men and a difference of about 8.5 per cent among the women. The higher rates evidently go with the more strenuous activities but it is quite possible that the diet may be a factor.

TABLE 23.—TAKAHIRA'S GROUPS ARRANGED ACCORDING TO THE AVERAGE METABOLISM.*

<i>Men:</i>	
8 General laborers	+5.84
10 Policemen	+3.36
11 Miscellaneous	+1.10
9 Skilled laborers	-1.19
9 Barbers	-1.40
11 Motormen and street car conductors	-1.59
11 School teachers	-2.90
Tradesmen	-6.87
<i>Women:</i>	
16 Stenographers	+3.69
11 Miscellaneous, mostly laborers	+3.61
16 School teachers	-4.82

* Averages of comparisons with the Sage, Harris-Benedict and Dreyer standards.

Lauter³ who studied a number of heavy athletes obtained satisfactory results on seven. The average heat production

¹ Benedict and Smith: Jour. Biol. Chem., 1915, 20, 243.

² Gephart and Du Bois: Clin. Cal. 13, Arch. Int. Med., 1916, 17, 902.

³ Lauter: Deutsch. Arch. f. klin. Med., 1926, 150 315.

was 41.3 calories per square meter per hour, a figure distinctly higher than the averages for non-athletes.

The Influence of Sleep.—Our evidence regarding the influence of sleep on metabolism is somewhat contradictory. Loewy¹ found no diminution in oxygen consumption during natural sleep though there was a diminution in the sleep following morphine. Johansson² who studied his own carbon dioxide excretion found no difference between sleep and the state of complete muscular relaxation which he has mastered so perfectly. On the other hand, Benedict³ demonstrates very clearly that the metabolism of his subject Levanzin, during a thirty-one-day fast, was consistently lower when asleep at night in the calorimeter than during the morning hours when he was studied by means of the "unit" respiration apparatus. The muscular activity was no greater when awake but it is possible that the difference in apparatus and in time of day may have had some influence. The average difference between sleeping and waking was 13.2 per cent, on two days it was over 20 per cent.

Both Benedict⁴ and Talbot⁵ in their recent publications speak of a marked fall in metabolism when a patient falls asleep. There is also a drop in the pulse rate and in the respiratory quotient. The cause of this change in quotient is not clear. One would not expect the organism to change suddenly the proportions in which it oxidized fat and carbohydrate.

¹ Loewy: Berlin. klin. Wchnschr., 1891, No. 18, p. 437.

² Johansson: Shand. Arch. f. Physiol., 1898, 8, 85.

³ Benedict: Carnegie Institution of Washington Publication No. 203, 1915, p. 343; Jour. Biol. Chem., 1915, 20, 263.

⁴ Benedict: Lectures on Nutrition, Mayo Foundation Lectures, Saunders & Co., Philadelphia and London, 1924-1925, 1, 7.

⁵ Talbot: Physiol. Rev., 1925, 5, 477.

CHAPTER VIII.

THE SELECTION OF NORMAL STANDARDS.

WE have now reached a point where we can analyze the data regarding the basal metabolism and attempt to select the normal standards which will be most serviceable in the study of patients. Krogh is perfectly correct in emphasizing the fact that we never determine the true basal metabolism because we do not obtain the minimal metabolism. In order to do this we should have to examine our patients during profound sleep in the dead of night after a long period of undernourishment. After all, the true minimal metabolism of the resting tissues could be obtained only if we stopped the heart, respiration, and all the glandular activities. Krogh's term of "standard metabolism" applied to what we now call "basal" is an excellent one, but it has not yet gained general acceptance, and physiologists and clinicians still cling to the original nomenclature, knowing perfectly well all its limitations.

Let us first tabulate the various factors which have been rigorously excluded or taken into account in basal metabolism tests (Tables 24 and 25).

TABLE 24, A.—FACTORS EXCLUDED IN ALL BASAL TESTS ON NORMAL CONTROLS.

1. Muscular movements during the test (except a few minimal movements).
2. Recent muscular exertion (within a half to one hour).
3. Food within twelve to fourteen hours (except small non-stimulating breakfasts).
4. Strong emotions, noises, discomforts, etc.
5. Extremes of environmental temperature.
6. Disease.

B.—FACTORS TAKEN INTO ACCOUNT IN THE INTERPRETATION OF DETERMINATIONS OF THE BASAL METABOLISM.

1. Age.
2. Sex.
3. Weight.
4. Height.
5. Surface area or other formulas which depend on weight and height.
6. Undernutrition or overnutrition.
7. Athletic training.
8. Climate and altitude.
9. Sleep.
10. Body temperature.

TABLE 25.—ADDITIONAL FACTORS THE IMPORTANCE OF WHICH HAS BEEN RECENTLY RECOGNIZED OR SUGGESTED.

1. Occupation: laborers have a higher metabolism than those who lead sedentary lives.
2. Race, since the normal standards may be lower for Orientals or those living in the tropics.
3. Previous diet: a diet rich in protein seems to be associated with a higher basal level. The lowest figures according to Krogh are obtained after a diet rich in carbohydrate.
4. Menstruation: allowance for the premenstrual rise in metabolism found in some women.
5. Environmental temperature, with a more rigorous avoidance of cold or extremes of heat and humidity.
6. Minor emotions, such as last for several minutes after loud noises.
7. The effect of novelty, which in many instances raises the metabolism 5 per cent or so in the first test.
8. Strenuous exertions or emotions on the day before the test.
9. Exclusion of all except minimal figures. Since there are no extraneous factors except disease, undernutrition, and sleep, which depress the metabolism, it is suggested that the lowest two tests which agree closely represent the true basal.
10. Time of year.

In addition we must remember that there are differences of 2 to 5 per cent in the various types of apparatus, calculations, and experimental procedures. Long experiments in calorimeters and respiration chambers seem to give somewhat higher results than short periods. The spirometer experiments seem also to give figures a little higher than the closed circuit types of graphic apparatus filled with air which has been enriched by oxygen. Finally, we must emphasize the fact that leaks and other manifestations of poor technic cause more trouble than any of the factors above enumerated.

The Search for Normal Standards.—Most of the older investigators expressed their experimental results in terms of cubic centimeters of oxygen and carbon dioxide per kilogram of body weight and minute. We have spoken on page 129 of the objections to this method and the desirability of converting the figures into calories for a certain unit of time, preferably the hour. It was in former times the custom to compare each patient with the average obtained on a group of three or four normal men of about the same age and size. Some investigators followed Rubner's lead and expressed their results in terms of calories per square meter of body surface, using Meeh's formula

$$\text{Surface area} = 0.12312\sqrt{W^2}$$

Thus McCrudden and Lusk¹ in 1913, made some careful observations on a dwarf, aged seventeen years, 113.3 cm.

¹ McCrudden and Lusk: Jour. Biol. Chem., 1913, 13, 447.

high, weighing 21.3 kilograms, of a type described by Herter as intestinal infantilism. They compared the basal metabolism per square meter of body surface per day with that of two dogs studied in the same calorimeter and several men studied in Benedict's calorimeter. The results are given below in Table 26.

TABLE 26.

Subject.	Weight.	Cal. per sq. m. (Meeh) per day.
Dwarf, J. P.	21.3	775
Dog I	21.8	759
Dog II	9.3	784
Average 4 men	789

TABLE 27.—AVERAGE OF 48 NORMAL CONTROLS FROM VARIOUS SOURCES GROUPED ACCORDING TO BODY WEIGHT.

Weight (kg.).	Number of subjects.	Average calories.	
		Per kg. hr. 24 hrs.	Per sq. m. body surface per hour (Meeh's formula)
40 to 50	6	27.9	33.6
50 to 60	17	26.5	34.1
60 to 70	15	25.5	34.5
70 to 80	4	23.9	34.1
80 to 90	6	21.7	32.3

In 1914 Coleman and Du Bois¹ prepared some normal standards by means of which they might ascertain the changes in metabolism found in typhoid patients. They gathered together 27 normal controls from the works of Benedict and his collaborators; 19 from Loewy and Magnus-Levy and added 2 of their own. The results are shown in Table 27. They found that the average heat production per square meter (Meeh) per hour was 34.2 calories with a variation 10 per cent above or 10 per cent below this point. It became quite evident that the largest error in the standard was introduced by Meeh's formula and in the next two years the Russell Sage Institute of Pathology in New York published a series of papers based on the new surface area method worked out in their laboratory by D. Du Bois.^{2, 3, 4, 5} It was found that the results showed less variation when the surface was measured by the more accurate new methods. Table 28

¹ Coleman and Du Bois: Arch. Int. Med., 1914, 14, 168.

² Du Bois, D., and Du Bois, E. F.: Clin. Cal. 10, Arch. Int. Med., 1916, 17, 863.

³ Gephart and Du Bois: Clin. Cal. 4, Arch. Int. Med., 1915, 15, 835.

⁴ Du Bois: Clin. Cal. 12, Arch. Int. Med., 1916, 17, 887.

⁵ Gephart and Du Bois: Clin. Cal. 13, Arch. Int. Med., 1916, 17, 902.

TABLE 28.—A COMPARISON OF THE METABOLISM OF FAT AND THIN SUBJECTS TAKEN LARGELY FROM THE WORK OF BENEDICT, EMMES, ROTH AND SMITH.

Name.	Deviation from normal average, per cent.		Calories per kg. per 24 hours.	Name.	Deviation from normal average, per cent.		Calories per kg. per 24 hours.
	34.7, Meeh's formula.	39.7, height-weight formula.			32.3, Meeh's formula.	36.9, height-weight formula.	
FAT MEN.				FAT WOMEN.			
W. S.	- 1.2	+ 5.0	22.8	Dr. M.D.	-11.2	- 1	18.9
O. F. M.	- 8.6	- 0.5	21.3	O. A.	- 9.6	0	19.5
Prof. C.	-15.1	-12.0	19.9	H. H.	-17.0	- 7	18.0
F. E. M.	- 6.9	- 4.0	22.7	H. D.	-10.3	+ 1	20.1
F. A. R.	- 6.1	- 3.0	22.9	F. M. R. ⁶	- 6.8	+ 7	21.0
				D. L. ⁶	-13.5	+ 1	19.7
				F. F. W. ⁶	-16.9	0	18.6
Average	- 7.6	- 4.0	21.9	...	-12.2	0	19.4
THIN MEN.				THIN WOMEN.			
R. A. C.	+11.3	2.0	29.7	J. T.	+12.5	+ 2	31.7
B. N. C.	+ 7.2	- 6.0	29.8	A. A.	+ 9.6	- 5	32.0
L. E. A.	+ 7.6	- 2.0	29.5	E. W.	-12.2	+ 7	31.5
A. F. G.	- 0.8	-10.0	27.0	A. C.	- 0.5	- 8	27.4
				J.	- 2.1	- 7	26.9
				L. B.	- 6.7	-13	24.9
Average	+ 6.4	- 5.0	29.0	...	+ 4.2	- 4	29.1

⁶ Mean's subjects.

was compiled from the subjects of Benedict, Emmes, Roth and Smith and those of Means who were more than 20 per cent under or overweight according to a table compiled by the insurance companies showing the average weight of male applicants between the ages of twenty-five and twenty-nine years. It will be seen that there is a great difference between the groups according to calories per kilogram, less according to Meeh's formula and only 5 per cent according to the height-weight formula. Takahira¹ in his study of a large number of normal Japanese has demonstrated the same thing. The group of 10 men who were heavy for their height gave an average for their basal metabolism 0.3 per cent above the average according to the height-weight surface area formula but 11 per cent below the average according to weight alone.

Means² had already shown, in 1915, that in the case of a very obese woman the metabolism, according to Meeh's formula, was 23.9 calories per square meter per hour but was

¹ Takahira: Rep. of Metab. Lab. Imp. Govt. Inst. for Nutrition, Tokyo, 1925, 1, No. 1.

² Means: Jour. Med. Res., 1915, 32, 121; Jour. Biol. Chem., 1915, 21, 263.

34.8, very close to the normal average, when measured by the new Sage formula. About the same figures were found by him in a second case of obesity. Means also obtained a slightly smaller variation with his normal controls using the new formula. Aub and Du Bois¹ tried to obtain more information on this question by studying the metabolism of two men whose legs had been amputated and several dwarfs of various types. For our present purposes we must exclude the dwarfs showing endocrine involvement and the dwarf who was nauseated while in the calorimeter. The results on the others are shown in the following table (Table 29).

TABLE 29.—BASAL METABOLISM OF DWARFS AND LEGLESS MEN.

Name.	Condition.	Age.	Weight, kg.	Calories per kg. per hour.	Calories per sq. m., linear formula.
H. J. . .	Legless man	35	54.6	1.01	41.3
R. L. . .	Legless man	43	63.8	0.92	41.3
P. W. . .	Rachitic dwarf	38	37.3	1.32	41.0
R. de P. . .	Achondroplasia	35	40.9	1.28	42.2

This merely confirms the work which Rubner² performed many years ago with a small dwarf.

In 1917 Aub and Du Bois, at the end of their article reporting the basal metabolism of old men added the following note:

"At the suggestion of Drs. Means and Boothby, a set of normal standards for various ages has been calculated from the age curve published in this paper and Lusk's 'Science of Nutrition,' third edition, 1917. These will be used in the Sage publications after the present series, until changes in the curve are made by the addition of new data. The figures for females are calculated as 7 per cent below the average for males, more data, however, being desirable to establish for the female sex the general validity of this method of computation.

TABLE 30.—CALORIES PER SQUARE METER OF BODY SURFACE PER HOUR (HEIGHT-WEIGHT FORMULA).

Age, years.	Males.	Females.
14 to 16	46.0	43.0
16 to 18	43.0	40.0
18 to 20	41.0	38.0
20 to 30	39.5	37.0
30 to 40	39.5	36.5
40 to 50	38.5	36.0
50 to 60	37.5	35.0
60 to 70	36.5	34.0
70 to 80	35.5	33.0

¹ Aub and Du Bois: Clin. Cal. 21, Arch. Int. Med., 1917, 19, 842.

² Rubner: Biologische Gesetze, Marburg, 1887, p. 10.

In 1919 Harris and Benedict¹ published their classical biometric study of basal metabolism, giving the data and analyses on which practically all the subsequent discussions of this subject have been based. The material for analysis consisted of the figures for the basal metabolic rates of nearly 250 adults and about 100 infants, as determined by Dr. Benedict and his associates. The analyses were made by modern statistical methods, paying particular attention to the correlation coefficients, and the reader is referred to their second chapter for an excellent discussion of the methods employed. With great labor and patience they treated statistically most of the factors associated with basal metabolism and endeavored to find without any preconceived ideas as to theory those formulæ which would most nearly predict the heat production of the normal control. Their results are referred to in many other places in my book, particularly in the chapter which deals with theories. Their final conclusion was that the best formulæ for the prediction of the basal metabolism were the following:

For men—

$$h = +66.4730 + 13.7516w + 5.0033s - 6.7550a$$

For women—

$$h = +655.0955 = 9.5634w + 1.8496s - 4.6756a$$

when h equals total heat production per twenty-four hours, w , weight in kilograms; s , stature in centimeters, and a , age in years.

The calculations seem rather formidable, but in practice they are very simple since tables have been published by Harris and Benedict, Carpenter,² and Benedict.³ An abbreviated table giving the results in the period of one hour rather than one day has been made by Roth⁴ and is reproduced below:

¹ Harris, J. A., and Benedict, F. G.: A Biometric Study of Basal Metabolism in Man, Carnegie Institution of Washington, 1919, Pub. No. 279.

² Carpenter: Tables, Factors and Formulas for Computing Respiratory Exchange and Biological Transformations of Energy, Carnegie Institution of Washington, 1921, Pub. No. 303.

³ Benedict, F. G.: In Abderhalden's Handbuch der biologischen Arbeitsmethoden, Urban and Schwarzenberg, Berlin, 1924, 4, pt. 10, 415.

⁴ Roth: Metabolimetric Chart. See also Roth's Metabolimetric Compendium, P. B. Hoeber, New York, 1924.

TABLE 31.—NORMAL STANDARDS.

DIRECTIONS.

Harris-Benedict: The predicted calories per hour are obtained by adding the calories corresponding to the weight in kilograms (*A*) to the calories corresponding to age and stature (*B*, *C*, *D*).

Benedict Standards for Girls Twelve to Eighteen: The predicted calories are given per kilogram of body weight per hour according to age.

Dreyer: The predicted calories are based on weight and age. Greater accuracy may be obtained by correcting the value for weight according to Dreyer's method. For females, subtract 10 per cent.

Interpolation: In the use of these condensed tables, interpolation is necessary.

A: Harris-Benedict Standards Based on Body Weight.

Weight,			Cal. per hr.			Weight,			Cal. per hr.		
kg.	Males.	Females.				kg.	Males.	Females.			
10	8.5	..				72	44.0	56.0			
12	9.7	..				74	45.2	56.8			
14	10.8	..				76	46.3	57.6			
16	12.0	..				78	47.5	58.4			
18	13.1	..				80	48.6	59.2			
20	14.3	..				82	49.7	60.0			
22	15.4	..				84	50.9	60.8			
24	16.6	..				86	52.0	61.6			
26	17.7	37.6				88	53.2	62.4			
28	18.8	38.4				90	53.3	63.2			
30	19.9	39.2				92	55.5	64.0			
32	21.1	40.0				94	56.6	64.8			
34	22.2	40.8				96	57.8	65.6			
36	23.4	41.6				98	58.9	66.4			
38	24.5	42.4				100	60.1	67.2			
40	25.7	43.2				102	61.2	68.0			
42	26.8	44.0				104	62.4	68.8			
44	28.0	44.8				106	63.5	69.6			
46	29.1	45.6				108	64.7	70.4			
48	30.3	46.4				110	65.8	71.2			
50	31.4	47.2				112	67.0	72.0			
52	32.6	48.0				114	68.1	72.8			
54	33.7	48.8				116	69.3	73.6			
56	34.9	49.6				118	70.4	74.4			
58	36.0	50.4				120	71.6	75.2			
60	37.2	51.2				122	72.7	76.0			
62	38.3	52.0				124	73.9	76.8			
64	39.5	52.8				126	75.0	77.6			
66	40.6	53.6				128	76.1	78.4			
68	41.8	54.4				130	77.2	79.2			
70	42.9	55.2									

B: Harris-Benedict Standards Based on Age and Stature — Men.

Cm.	Age 20	25	30	35	40	45	50	55	60	65	70
150	25.6	24.2	22.8	21.4	20.0	18.6	17.2	15.8	14.4	13.0	11.6
155	26.6	25.2	23.8	22.4	21.0	19.6	18.2	16.8	15.4	14.0	12.6
160	27.7	26.3	24.9	23.5	22.1	20.7	19.3	17.9	16.5	15.1	13.7
165	28.7	27.3	25.9	24.5	23.1	21.7	20.3	18.9	17.5	16.1	14.1
170	29.8	28.4	27.0	25.6	24.2	22.8	21.4	20.0	18.6	17.2	15.8
175	30.8	29.4	28.0	26.6	25.2	23.8	22.4	21.0	19.6	18.2	16.8
180	31.9	30.4	29.1	27.6	26.2	24.8	23.4	22.0	20.6	19.2	17.8
185	32.9	31.5	30.1	28.7	27.3	25.9	24.5	23.1	21.7	20.3	18.9
190	34.0	32.5	31.2	29.7	28.3	26.9	25.5	24.1	22.7	21.3	19.9
195	35.0	33.6	32.2	30.8	29.4	28.0	26.6	25.2	23.8	22.4	21.0
200	36.1	34.6	33.2	31.8	30.4	29.0	27.6	26.2	24.8	23.4	22.0

C: Harris-Benedict Standards Based on Age and Stature — Women.

Cm.	Age 20	25	30	35	40	45	50	55	60	65	70
150	7.7	6.7	5.7	4.7	3.8	2.8	1.8	.9	0.0	-1.0	-2.0
155	8.1	7.1	6.1	5.1	4.2	3.2	2.2	1.2	.2	-.7	-1.7
160	8.5	7.5	6.5	5.5	4.5	3.6	2.6	1.6	.6	-.3	-1.3
165	8.8	7.8	6.9	5.9	4.9	4.0	3.0	2.0	1.0	.0	-.9
170	9.2	8.2	7.3	6.3	5.3	4.3	3.4	2.4	1.4	.5	-.5
175	9.6	8.6	7.6	6.7	5.7	4.7	3.7	2.8	1.8	.8	-.2
180	10.0	9.0	8.0	7.0	6.1	5.1	4.1	3.2	2.2	1.2	.2
185	10.4	9.4	8.4	7.5	6.5	5.5	4.5	3.5	2.6	1.6	.6
190	10.8	9.8	8.8	7.8	6.8	5.9	4.9	3.9	3.0	2.0	1.0
195	11.2	10.2	9.2	8.2	7.2	6.2	5.3	4.3	3.3	2.4	1.4
200	11.5	10.5	9.6	8.6	7.6	6.7	5.7	4.7	3.7	2.7	1.8

D: Harris-Benedict Standards Based on Age and Stature — Boys.

Cm.	Age 10	15	20	Kg.	Age 10	15	20
100	18.0	16.6	15.2	155	29.5	28.1	26.6
105	19.0	17.7	16.3	160	30.5	29.1	27.7
110	20.0	18.7	17.3	165	31.5	30.1	28.7
115	21.0	19.7	18.3	170	32.6	31.2	29.8
120	22.1	20.8	19.4	175	33.6	32.2	30.8
125	23.2	21.8	20.4	180	34.7	33.3	31.9
130	24.2	22.9	21.5	185	35.7	34.3	32.9
135	25.3	23.9	22.5	190	36.8	35.4	34.0
140	26.3	25.0	23.6	195	37.8	36.4	35.0
145	27.4	26.0	24.6	200	38.9	37.4	36.1
150	28.4	27.0	25.6				

E: Benedict-Talbot Standards for Boys and Girls.
Cal. per hr. from body weight.

Weight, kg.	Boys, cal.	Girls, cal.	Weight, kg.	Boys, cal.	Girls, cal.
3	6.3	6.3	31	47.5	44.6
4	8.8	9.2	32	48.3	45.4
5	11.3	11.9	33	49.2	46.4*
6	13.8	14.6	34	50.0	47.3*
7	16.3	16.9	35	50.8	48.3*
8	18.5	19.2	36	51.7	49.2*
9	20.6	20.8	37	52.3	50.1*
10	22.7	22.5	38	53.1	50.7
11	24.6	24.2	39		50.8
12	26.0	25.4	40		51.0
13	27.5	26.7	41		51.2
14	29.0	27.7	42		51.3
15	30.2	28.8	43		51.4
16	31.5	29.6	44		51.6
17	32.5	30.6	45		51.7
18	33.5	31.7	46		51.8
19	34.6	32.5	47		52.0
20	35.8	33.5	48		52.1
21	36.9	34.6	49		52.3
22	37.9	35.6	50		52.4
23	39.2	36.7	51		52.5
24	40.2	37.5	52		52.7
25	41.3	38.8	53		52.8
26	42.5	39.6	54		52.9
27	43.5	40.6	55		53.1
28	44.6	41.7	56		53.2
29	45.4	42.5	57		53.3
30	46.5	43.5	58		53.5

For boys apply Harris-Benedict Standards: A + D.

* Figures obtained by interpolation. Not in original.

F: Dreyer Standard for Men.

Kg.	Age 15	20	25	30	35	40	45	50	55	60	65	70	75	80
25	45.2	43.5	42.3	41.2	40.4	39.7	39.0	38.5	38.0	37.5	37.1	36.8	36.5	36.2
30	49.5	47.6	46.3	45.2	44.2	43.5	42.8	42.2	41.7	41.2	40.7	40.3	39.8	39.6
35	53.5	51.5	50.0	48.8	47.8	46.9	46.2	45.6	45.0	44.5	44.0	43.6	43.2	42.8
40	57.1	55.0	53.5	52.1	51.1	50.2	49.4	48.8	48.1	47.5	47.0	46.6	46.2	45.8
45	60.1	58.4	56.7	55.3	54.2	53.3	52.4	51.7	51.1	50.5	50.0	49.5	49.0	48.6
50	64.9	61.6	59.7	58.4	57.1	56.1	55.3	54.5	53.8	53.2	52.6	52.1	51.6	51.2
55	66.7	64.6	62.7	61.2	59.9	58.0	58.0	57.2	56.4	55.8	55.2	54.6	54.1	53.7
60	70.1	67.5	65.5	63.9	62.6	61.5	60.6	59.7	58.9	58.3	57.7	57.0	56.6	56.1
65	72.5	70.2	68.1	66.5	65.1	64.0	63.0	62.2	61.4	60.6	60.0	59.5	58.9	58.3
70	75.6	72.9	70.7	69.0	67.7	66.4	65.4	64.5	63.7	63.0	62.2	61.6	61.1	60.5
75	78.3	75.4	73.3	71.4	70.0	68.7	67.7	66.8	65.9	65.2	64.5	63.8	63.3	62.7
80	80.9	77.9	75.6	73.8	72.3	70.0	69.9	68.9	68.0	67.2	66.5	65.9	65.3	64.7
85	83.4	80.3	78.0	76.1	74.5	73.2	72.1	71.0	70.2	69.3	68.6	67.9	67.3	66.7
90	85.7	82.6	80.2	78.1	76.7	75.3	74.1	73.1	72.2	71.3	70.6	69.9	69.3	68.7
95	88.1	84.4	82.3	80.4	78.7	77.4	76.2	75.1	74.2	73.3	72.4	71.8	71.2	70.5
100	90.4	87.1	84.4	82.5	80.8	79.4	78.2	77.0	76.1	75.2	74.4	73.7	73.0	72.4
105	92.5	89.2	86.6	84.5	82.8	81.3	80.0	79.0	77.5	77.0	76.3	75.5	74.8	74.2
110	94.8	91.4	88.6	86.4	84.8	83.3	82.0	80.9	79.8	78.9	78.1	77.3	76.6	75.9
115	97.0	93.4	90.7	88.6	86.7	85.2	83.9	82.6	81.6	80.7	79.8	79.0	78.2	77.6
120	99.1	95.4	92.7	90.3	88.6	87.0	85.7	84.4	83.3	82.4	81.5	80.7	79.9	79.3

In 1920 Dreyer¹ recalculated the data of Harris and Benedict and came to the following conclusions:

"The formula $\frac{W^n}{C_x A^{0.1333}} = K$ where n is approximately 0.5 and $K = 0.1015$ in males and 0.1127 in females, expresses the basal metabolism in an extremely satisfactory manner over a wide range of body, size, and age and indicates that basal metabolism is not a simple function of the body surface." W equals net body weight in grams, C , total calories produced in twenty-four hours; A , age in years. He adds: "The deviations in the case of the author's formula will be considerably reduced if trunk, length, and chest circumference were considered. The actual data on this point will be published later."

I have been unable to find this promised data of Dreyer's, but the matter has been investigated by Hobson, in² Dreyer's laboratory in Oxford, and by Stoner,³ in Philadelphia. Hobson states that for males living a healthy, active life, with opportunities for physical recreation, the K in Dreyer's formula will be found to be approximately 0.0990 instead of 0.1015. Stoner makes the calculations easy by giving

¹ Dreyer: *Lancet*, 1920, ii, 289.

² Hobson: *Quart. Jour. Med.*, 1923, 16, 363.

³ Stoner: *Boston Med. and Surg. Jour.*, 1923, 189, 236, 239; *Ibid.*, 1924, 191, 1026, 1030.

extended tables, not only for Dreyer's first formula, but also for the two formulæ which give the theoretic weight based upon sitting height or chest circumference. These are, according to Stoner

$$W\lambda = \frac{0.319}{\sqrt{0.38025\lambda}}$$

$$Wch = \frac{0.365}{\sqrt{0.662ch}}$$

In which $W\lambda$ equals theoretic weight in grams based, upon sitting height in cubic centimeters (λ), and Wch equals theoretic weight in grams based upon chest circumference in cubic centimeters (ch).

Dreyer¹ has given specific directions as to the method for taking the necessary measurements. For λ : "The subject places the backs of the fingers upon the platform on which he sits, and, with the fingers pointing backward and the knees flexed, lifts the lower portion of the body gently backward until the lowest bony portion of the os sacrum is in contact with the front of the measuring standard. The back is then straightened until the back of the head comes into contact with the standard. It will be found that different persons require to bend the knees in different degrees in order to achieve this position. The head should be tilted neither up nor down, and the eyes should look straight forward. The measurement thus obtained gives the distance between the ischial tuberosities and the top of the head."

Ch is measured at the nipple level in the male; just below the breasts in the female.

In 1923 August Krogh stated: "The Harris-Benedict prediction-tables for the 'basal' metabolism are very reliable for average subjects but, owing to their statistical nature, less so for persons of exceptional build or higher age. The Du Bois method and table for computing the basal metabolism give results which are on an average too high (about 4 per cent or more) but they are less likely to fail when used on exceptional subjects."

In 1925 tables appeared in a pamphlet connected with Krogh's² respiration apparatus which give the Harris-Benedict

¹ Dreyer and Hanson: The Assessment of Physical Fitness, Hoeber, New York, 1921.

² Krogh's Recording Respiration Apparatus—Tables of Normal Metabolic Rates after Du Bois and Benedict-Harris, J. H. Schultz, Copenhagen, 1925.

standards in calories per minute and also the Sage (Aub-Du Bois) standards for the ages of fifteen to seventy-five years, with a uniform 6 per cent reduction (Table 32).

TABLE 32.—KROGH'S MODIFICATION OF THE SAGE (AUB-DU BOIS) STANDARDS.

Age.	Men.		Women.	
	Calories per min.	Calories per hr.	Calories per min.	Calories per hr.
15 to 16	0.707	42.4	0.658	39.5
16 to 17	0.689	41.35	0.638	38.3
17 to 18	0.672	40.3	0.620	37.2
18 to 19	0.657	39.4	0.606	36.4
19 to 20	0.646	38.8	0.599	35.9
20 to 22	0.637	38.2	0.590	35.4
22 to 24	0.631	37.9	0.584	35.0
24 to 26	0.623	37.4	0.580	34.8
26 to 30	0.615	36.9	0.575	34.5
30 to 35	0.609	36.5	0.570	34.2
35 to 40	0.606	36.4	0.565	33.9
40 to 45	0.603	36.2	0.560	33.6
45 to 50	0.600	36.0	0.555	33.3
50 to 55	0.592	35.5	0.550	33.0
55 to 60	0.585	35.1	0.542	32.5
60 to 65	0.577	34.6	0.535	32.1
65 to 70	0.568	34.1	0.528	31.7
70 to 75	0.558	33.5	0.518	31.1

The standards of Aub and Du Bois published in 1917 were based on their own studies of old men, on the various Sage papers on "Clinical Calorimetry" published in 1915 and 1916, and particularly on Paper 12 of this series¹ in which the author had constructed curves from data taken chiefly from the earlier work of Benedict and his collaborators but including the data of Magnus-Levy, Murlin, Palmer, Means, and Gamble, as well as the Sage calorimeter data. It has become quite apparent that the "basal requirements" of the earlier investigators were not as strict as they became later between 1916 and 1923. This is probably the reason that the Aub and Du Bois figures, as noted by Means and Woodwell² run about 0.6 to 1.8 calories per hour higher than the Harris-Benedict and Dreyer standards which are founded on the short period experiments of the Nutrition Laboratory of Boston.

Krogh has for several years been insisting on even stricter requirements than those usually employed. He demands a

¹ Du Bois: Clin. Cal. 12, Arch. Int. Med., 1916, 17, 887.

² Means and Woodwell: Arch. Int. Med., 1921, 27, 608.

previous diet low in protein, rich in carbohydrate, and repeated short period tests until minimal figures are obtained. It is therefore obvious that we cannot compare his standards with the others until we have data obtained by his methods in sufficient mass to permit of careful analysis.

There are now in the literature many comparisons of the Sage, Harris-Benedict, and Dreyer standards, but this does not tell us which method is theoretically or practically preferable.

Dreyer's first formula ignores the height, but of the two supplementary formulæ one is based on sitting height and the other on the chest circumference.

All of the standards, Sage, Harris-Benedict, and Dreyer call for a diminution in metabolism with age and the slopes of the curves are not very different. For all these reasons we should expect a close agreement in all three methods particularly as they are all based chiefly on the data of the Nutrition Laboratory in Boston.

Thus, Harris and Benedict (p. 201) found but little difference between the errors of prediction according to surface area as estimated from the height-weight chart and their own formulæ, and they pointed out that both methods use height and weight as factors. Dreyer,¹ in comparing the three methods, found the following average percentage of deviations between calculated and observed:

Method.	Males.	Females.
Dreyer	5.27	6.33
Benedict	5.33	6.39
Du Bois	5.65	7.53

Means and Woodwell² have compared the three methods and have concluded "that the average deviation was essentially the same by each, though the Du Bois deviations tended to run about two points or more lower than either of the others." They also note that "this difference can be abolished by a slight change in the Sage standards. These standards are probably too high by somewhere between 1.8 and 0.6 calories." They say, "It is suggested that, although the deviations by the three methods are very similar, nevertheless, it is desirable to have uniformity, and that, therefore, the Du Bois method be continued, since it already is in com-

¹ Dreyer: *Lancet*, 1920, ii, 289.

² Means and Woodwell: *Arch. Int. Med.*, 1921, 27, 608.

mon use and the others appear to possess no material advantage over it."

Boothby and Sandiford¹ noted the parallelism between the Sage and Harris-Benedict methods, but found that their normals agreed more closely with the former, as shown in Tables 33 and 34. The same difference was observed in those patients who were suffering from diseases which are supposed not to affect the metabolism.

TABLE 33.—SUMMARY BY DECADES OF THE ESSENTIAL DATA ON 102 NORMAL PERSONS. (BOOTHBY AND SANDIFORD.)

Decade.	Total No. of cases.	Height, cm.	Weight, kg.	Surface area.		Basal metabolic rate.	
				Du Bois, sq. m.	Harris and Benedict, sq. m.	Du Bois, per cent.	Harris and Benedict, per cent.
Females:							
21 to 29 . . .	19	161.3	59.1	1.61	1.60	+0.9	+ 2.3
30 to 39 . . .	24	160.5	59.3	1.61	1.60	-0.4	+ 3.6
40 to 49 . . .	7	163.4	71.4	1.76	1.74	-2.1	+ 3.6
50 to 59 . . .	9	161.8	60.9	1.63	1.62	+1.4	+ 7.4
60 to 69 . . .	2	156.5	46.6	1.43	1.46	+7.5	+15.5
Average	61	161.2	60.4	1.62	1.61	+0.3	+ 4.2
Males:							
21 to 29 . . .	15	172.0	64.7	1.76	1.76	+4.8	+ 6.3
30 to 39 . . .	14	171.6	65.6	1.76	1.77	-1.4	+ 3.8
40 to 49 . . .	5	175.0	73.5	1.88	1.91	+3.0	+ 8.6
50 to 59 . . .	6	173.5	67.5	1.80	1.81	-4.5	+ 4.8
60 to 69 . . .	1	169.5	53.2	1.61	1.59	+2.0	+16.0
Average	41	172.4	66.2	1.78	1.79	+1.0	+ 5.7
Average for males and females	102	165.7	62.8	1.69	1.68	+0.6	+ 4.8

Hobson,² working in the Department of Pathology at Oxford, has studied a number of normal men and boys. He suggests, as we have said before, a slightly lower value for K in the formula and he finds that from a theoretical and practical standpoint the calculated weight and not the observed weight should be employed in predicting the normal

¹ Boothby and Sandiford: Laboratory Manual of the Technic of Basal Metabolic Rate Determinations, Philadelphia and London, W. B. Saunders Company, 1920, p. 15.

² Hobson: Quart. Jour. Med., 1923, 16, 363.

metabolism for a given individual. He concludes that the Dreyer formula fulfils all the necessary criteria in a highly satisfactory manner from both theoretical and practical considerations and that it is an improvement upon the methods of Benedict and Du Bois in that it holds over a wider range of age and weight with greater accuracy and is based upon sounder principles. His comparisons are given in Table 35.

TABLE 34.—COMPARISON OF THE SURFACE AREA AND BASAL METABOLISM AS CALCULATED BY THE DU BOIS AND BY THE HARRIS AND BENEDICT METHODS IN 455 PERSONS.

Sex.	Total No. of cases.	Height, cm.	Weight, kg.	Surface area.		Basal metabolic rate.	
				Du Bois, sq. m.	Harris and Benedict, sq. m.	Du Bois, per cent.	Harris and Benedict, per cent.
Chronic nervous exhaustion:							
Females	222	162.4	53.8	1.56	1.55	+1.2	+ 5.0
Males	27	172.6	60.6	1.71	1.71	+1.0	+ 5.7
Males and females	249	163.5	54.6	1.57	1.56	+1.2	+ 5.1
Migraine:							
Females	27	161.3	55.2	1.56	1.56	-1.0	+ 3.1
Males	2	174.0	66.0	1.79	1.79	+3.5	+12.5
Males and females	29	162.1	56.0	1.58	1.57	-0.7	+ 3.8
Obesity:							
Females	61	161.9	96.1	1.99	2.00	-0.8	+ 1.5
Males	12	173.3	105.3	2.17	2.36	+0.1	- 3.9
Males and females	73	163.7	97.6	2.02	2.06	-0.7	+ 0.5
Normals:							
Females	61	161.2	60.4	1.62	1.61	+0.3	+ 4.2
Males	41	172.4	66.2	1.78	1.79	+1.0	+ 5.7
Males and females	102	165.7	62.8	1.69	1.68	+0.6	+ 4.8

TABLE 35.—HOBSON'S COMPARISON OF NORMAL STANDARDS. (APPLIED TO HIS SERIES OF 51 NORMAL MEN AND BOYS, USING ONLY OBSERVATIONS EXACTLY COVERED BY PUBLISHED TABLES.)

	Dreyer K = 0.1015.	Dreyer K = 0.0990.	Benedict.	Du Bois.
Mean percentage Δ . .	5.58	5.20	6.69	5.48
Individual mean \pm percent- age Δ	+3.07	+0.39	+5.45	+0.73
Number of observations .	46.0	46.0	32.0	39.0

Stoner¹ recommends that the older basal metabolism clinics in this country retain the Aub-Du Bois standards, since the

¹ Stoner: Boston Med. and Surg. Jour., 1923, 189, 236, 239.

adoption of later standards would make difficult the correlation of data obtained before and after the change. He finds that the Harris-Benedict prediction tables are coming more and more into use as the younger men and more recent clinics are installing clinical calorimetry departments. Stoner does not find much difference between the two when 4.2 or approximately 4 "points" (or per cent) are added to the Harris-Benedict standards. He says that it has become customary in some hospitals to center the normal physiological latitude on +5 (Harris-Benedict) rather than ± 0 . In his own laboratory he extends the customary 21 points of physiological latitude to 31 points, from -10 to +20, designating all results falling between these limits as not abnormal.

Stoner condemns certain hybrid tables published by Sanborn,¹ who subtracted 4 to 5 per cent from the Aub-Du Bois tables. He points out several errors in these modified tables and suggests that all results so calculated be excluded from the recognized legitimate data on this subject.

Stoner, in speaking of the Dreyer formula, mentions the unpublished analysis of Stoner and Cowan, who find in a series of 350 routine hospital determinations that the Harris-Benedict standards yield results 3.0 per cent above the Aub-Du Bois "normals" and that the Dreyer formulæ give rates 0.3 per cent above those of Harris and Benedict. Stoner² gives tables for estimating the metabolism of males according to the Dreyer formula and subtracts 10 per cent for the females. He also publishes tables for estimating the normal weight according to Dreyer's measurements of the sitting height or chest circumference, but he finds no advantage of theoretic over actual weight. In practice he does not report hospital metabolic rates in terms of Dreyer's standards. Root and Miles³ find that chest circumference is closely dependent on body weight and reflects temporary weight variations, especially in the obese, and conclude that it should not be used as a measure for predicting the normal weight. The trunk measurement seems to be somewhat more useful.

In Europe the Harris-Benedict prediction tables have been much used and have been found extremely satisfactory.

¹ Sanborn, F. B. (Editor): *Basal Metabolism: Its Determination and Application*, Boston, 1922, p. 238.

² Stoner: *Boston Med. and Surg. Jour.*, 1924, **191**, 1026, 1030.

³ Root and Miles: *Jour. Metabol. Res.*, 1922, **2**, 173.

Plaut¹ obtained good agreement, though her results on women between forty and fifty years of age were slightly higher. She even found that three dwarfs came close to the predicted figures. Liebesny² also says that the Harris-Benedict tables have been extraordinarily verified, especially for extreme values in obesity. In such cases he finds them superior to the Aub-Du Bois standards, while in other cases they agree closely.

Møller,³ in Denmark, found the following averages and adopted the Harris-Benedict standards.

	Number.	Harris-Benedict.	Du Bois.	Dreyer.
Men students	14	100.7	100.8	103.0
Women students and nurses	10	99.5	96.0	99.9

In this country Blunt and Dye,⁴ making 216 tests on 17 normal college women, two and sometimes three tests on each subject, found the average 4.1 per cent below the Harris-Benedict and 6.5 per cent below the Aub-Du Bois standards. Blunt and Bauer⁵ noted that the average for 19 young college women 11 to 26 per cent underweight was 1.3 per cent below the Harris-Benedict and 1.9 per cent below the Aub-Du Bois tables. MacLeod and Rose,⁶ in a study of 92 normal women, obtained values considerably lower than in any previous series, and therefore the results agreed more closely with Harris and Benedict and Dreyer than with Aub and Du Bois. They observed no correlation between pulse-rate and basal metabolism.

Takahira,⁷ in his exhaustive study of 120 Japanese men and women, seems to have obtained the closest results using the Dreyer method, next best according to the Aub-Du Bois, and the greatest variations with the Harris-Benedict (see Table 23, p. 163), but apparently adopted the surface area method with a slight change in constants. He found the basal metabolism of the women averaged 9 per cent lower than the men according to surface area.

¹ Plaut: *Deutsch. Arch. klin. Med.*, 1923, **142**, 266.

² Liebesny: *Biochem. Ztschr.*, 1924, **144**, 308.

³ Møller, E.: *Kliniske Undersøgelser over Basalstofskiftet ved Sygdomme i Skjoldbruskkirtlen*, Levin and Munksgaards Forlag, Copenhagen, 1925.

⁴ Blunt and Dye: *Jour. Biol. Chem.*, 1921, **47**, 69.

⁵ Blunt and Bauer: *Jour. Home Economics*, 1922, **14**, 171.

⁶ MacLeod and Rose: *Am. Jour. Physiol.*, 1925, **72**, 236.

⁷ Takahira: *Report of the Metabolic Laboratory, The Imperial Government Institute for Nutrition, Tokyo, January, 1925*, **1**, No. 1.

TABLE 36.—ACTUAL RESULTS WITH THEIR DEVIATIONS FROM PREDICTED VALUES. (MACLEOD AND ROSE.)

Age.	Number of persons.	Calories per square meter per hour.	Calories per kilo per hour.	Calories per 24 hours.	Deviations from predicted values.					
					Aub-Du Bois.		Harris-Benedict.		Dreyer.	
					Without regard to sign.	With regard to sign.	Without regard to sign.	With regard to sign.	Without regard to sign.	With regard to sign.
20-29	42	33.8 ± 0.25	23.0	1307	10.2	- 8.5	8.2	-5.4	8.1	-4.8
30-39	31	34.0 ± 0.29	23.1	1307	8.0	- 6.9	6.7	-2.4	7.2	-1.0
40-49	13	31.3 ± 0.57	20.2	1244	14.1	-12.9	10.2	-6.8	10.1	-4.8

TABLE 37.—DISTRIBUTION OF CASES WITH RESPECT TO AGREEMENT WITH PREDICTION VALUES.

Deviation, per cent.	Aub-Du Bois.		Harris-Benedict.		Dreyer.	
	Number of cases.	Per cent of total cases.	Number of cases.	Per cent of total cases.	Number of cases.	Per cent of total cases.
0 to 3	28	20.3	46	33.3	36	26.1
0 to 5	47	34.1	57	41.3	59	42.7
0 to 7	62	44.9	72	52.2	79	57.2
0 to 10	79	57.3	96	69.5	93	67.4
0 to 15	110	79.7	121	87.7	121	87.7

Standards for Children.—*New-born Children.*—Benedict and Talbot in 1915 devised the following formula for predicting the metabolism of new-born children:

$$-h = 1 \times 12.65 \times 0.103 \sqrt[3]{W^2},$$

in which h equals total calories for twenty-four hours; l , length in centimeters, and w , weight in kilograms. They employed Lissauer's formula for body surface. This is still recommended by Talbot in 1921 and Benedict in 1924.¹ Their formula for estimating the surface of children will be found on page 125 of this book. Murlin, Conklin, and Marsh² obtained an average of 29.16 calories per square meter (Lissauer) per hour on normal full term babies.

Older Children.—Talbot's³ curves for older children are given on pages 140 and 141. He finds that the majority of the children come within 10 per cent of the curve. Since very few children over the age of twelve years were studied, he warns that the age periods on his charts after twelve years should be taken only as temporary suggestions. Benedict⁴ in 1924 has changed somewhat his standards for girls and has recommended that from the first week in life until the age of twelve years the height be used as a standard and from twelve until twenty years the weight be used. The tables are reproduced (Tables 38 and 39) slightly modified in order to give the results in terms of calories per hour.⁵

¹ Benedict and Talbot: Carnegie Institution of Washington, Pub. No. 233, 1915, p. 108; Talbot: Am. Jour. Dis. Child., 1921, 21, 519; Benedict, F. G.: Proc. Am. Philosophical Soc., 1924, 63, 25.

² Murlin, Conklin and Marsh: Am. Jour. Dis. Child., 1925, 29, 1.

³ Talbot: Am. Jour. Dis. Child., 1921, 21, 519.

⁴ Benedict, F. G.: Proc. Am. Philosophical Soc., 1924, 63, 25.

⁵ The author is indebted to Dr. Paul Roth for the modification of Table 38. He has added to Benedict's original table the estimated results for 139 and 140 cm.

TABLE 38.—BASAL PER-HOUR HEAT PRODUCTION OF GIRLS (BENEDICT¹) FROM THE FIRST WEEK AFTER BIRTH TO TWELVE YEARS OF AGE, PREDICTED FROM HEIGHT.

Height, cms.	Predicted heat, cals.	Height, cms.	Predicted heat, cals.	Height, cms.	Predicted heat, cals.
48	5.08	79	24.29	110	32.04
49	5.67	80	24.42	111	32.42
50	6.25	81	24.63	112	32.83
51	6.88	82	24.79	113	33.21
52	7.42	83	24.92	114	33.63
53	8.08	84	25.08	115	34.04
54	8.67	85	25.21	116	34.50
55	9.25	86	25.29	117	34.88
56	9.83	87	25.42	118	35.29
57	10.42	88	25.50	119	35.71
58	11.17	89	25.63	120	36.08
59	11.79	90	25.71	121	36.46
60	12.50	91	25.83	122	36.88
61	13.25	92	25.96	123	37.25
62	13.83	93	26.08	124	37.67
63	14.58	94	26.25	125	38.13
64	15.29	95	26.54	126	38.54
65	16.00	96	26.83	127	38.96
66	16.71	97	27.13	128	39.38
67	17.42	98	27.46	129	39.83
68	18.13	99	27.79	130	40.21
69	18.83	100	28.13	131	40.63
70	19.50	101	28.54	132	41.04
71	20.13	102	28.88	133	41.46
72	20.83	103	29.17	134	41.88
73	21.50	104	29.63	135	42.33
74	22.08	105	30.00	136	42.75
75	22.63	106	30.42	137	43.21
76	23.21	107	30.83	138	43.63
77	23.63	108	31.21	139	44.05
78	23.96	109	31.63	140	44.47

We have already spoken of the studies of Miss Bedale and Miss MacLeod² on normal girls. If we average their results (Table 40) we obtain an average figure of about 42.4 calories from the ages of nine to thirteen and after that a considerable drop. If these figures are used as standards between eleven and fourteen years it is quite evident that the normal zone must be widened to include +20 and -20 or +25 and -25 in order to allow for the wide divergences in the two curves.

The results on boys between the ages of twelve and sixteen

¹ Benedict, Francis G.: Proc. Am. Philosophical Soc., vol. 63, No. 1, 1924. (Table reduced to "per hour" values.)

² Bedale: Proc. Roy. Soc., B., 1923, 94, 368; MacLeod: Studies of the Normal Basal Energy Requirement, Inaugural Dissertation, Columbia University, New York, 1924.

TABLE 39.—BASAL HEAT PRODUCTION PER KILOGRAM OF BODY WEIGHT PER HOUR PREDICTED FROM AGE, FOR GIRLS TWELVE TO TWENTY YEARS OF AGE. (BENEDICT.)

Age, years.	Predicted heat.
12	1.29
12½	1.24
13	1.19
13½	1.14
14	1.09
14½	1.04
15	0.992
15½	0.942
16	0.912
16½	0.908
17 to 20	0.908

TABLE 40.—NORMAL GIRLS STUDIED BY BEDALE AND MACLEOD CALORIES PER SQUARE METER PER HOUR.

Year.	Bedale.	MacLeod.	Average.
9	42.62		
10	40.90		
11	47.73	37.5	42.61
12	43.89	41.3	42.59
13	43.08	41.0	42.04
14	34.18(?)	36.6	35.39(?)
15	38.34		
16	36.96		
17	31.83		

years baffle all analysis. As far as I can tell, the only two studies which deal with any significant number of normal boys are the Sage Boy Scout papers¹ and the report of Miss Bedale. As we have said before, the first Boy Scout paper gives results which are considered by Benedict to be too high, and it is certainly true that there were some factors which would tend to raise the metabolism 5 per cent or possibly more. Some of Miss Bedale's averages are not much lower. Her figures are as follows:

Age.	Calories per square meter.	Number of individuals.
8	40.39	3
11	48.10	4
12	34.93	1
13	43.18	4
14	35.16(?)	2
15	40.13	3
16	44.43	2
18	46.27	1

¹ Du Bois: Clin. Cal. 12, Arch. Int. Med., 1916, 17, 887; Olmstead, Barr and Du Bois: Clin. Cal. 27, Ibid., 1918, 21, 621.

We need more studies at these ages.

The Choice of Standards.—It is obvious that the choice of standards is difficult and that it must be left to the individual investigator.

King,¹ in his monograph on basal metabolism, has said:

"It seems to me unnecessary to insist upon the interchangeability of standard normal figures obtained by different methods, and I believe that workers in metabolism would do better to select normal standards for their use from observations made under conditions as nearly as possible similar to those under which they plan to work."

I should like to add that the man who studies the metabolism of patients should also study a fairly large number of normal controls, using exactly the same technic in order to ascertain the standards which show the best results under the given conditions of experimentation. Perhaps we are shirking a duty in not trying to establish a new curve that could be recommended as a new standard. This would only make the confusion worse and no one, in reviewing the literature, would be quite certain as to which standard was used. Even at the present time there is great confusion, and many authors neglect to give any statement more detailed than the brief note that "the metabolism was +25 per cent," omitting all mention of the standard used. In such cases the reviewer can only guess. Usually he can guess correctly if he knows something about the laboratory from which the report is made. The English as a rule employ the Dreyer standards; the Germans and newer metabolic laboratories in this country employ the Harris-Benedict prediction tables; the older American metabolic laboratories, and even the newer ones in the zone around the Mayo Clinic, are prone to employ the Sage standards.

Personally I do not see that the Dreyer method possesses any material advantage over the Harris-Benedict, and suggest that reports on adults be made according to both the Sage (page 169) and Harris-Benedict standards (page 171). Grafe, one of the most experienced investigators, averages the two. It seems probable that the Krogh modification of the Sage standards will prove to be even better when Krogh's specifications are followed.

¹ King, J. T., Jr.: *Basal Metabolism*, Baltimore, Williams and Wilkins Company, 1924, p. 33.

CHAPTER IX.

THEORIES CONCERNING THE BASAL METABOLISM.

HAVING studied the many factors which influence the basal metabolism we are now in a position to consider some of the theories and speculations which have been applied to this phenomenon. In spite of the large amount of research we are still uncertain as to the reason for the relative uniformity of the metabolism in different individuals and the relative constancy in the same individual.

There is no question as to the need of some metabolism in the resting organism. Life cannot be maintained even in cold-blooded animals without the production of heat. The amount of heat is naturally greater in warm-blooded animals whose temperature is almost always above that of the surrounding air. The human body, at 37°C. , even if deprived of all circulation of blood, would lose heat to the air at ordinary temperatures quite rapidly in spite of the fact that the skin and subcutaneous fat are exceedingly poor conductors. We can obtain an approximate idea of this amount from the studies of Guillemot¹ and of Bouchut,² who found that cadavers cooled at the rate of 0.4° to 0.8°C. per hour. Lefèvre³ calculates that a dead body would lose 550 calories per twenty-four hours in summer and 1000 calories in winter. These figures are only rough approximations but they demonstrate the fact that the body is under the stern necessity of producing enough warmth to maintain the standard temperature. We must add to this loss through simple conduction the amount lost through the transportation of heat from the internal organs to the skin by means of the blood. We must also take into consideration the fact that about one-quarter of the total heat, about 400 calories a day, is lost through the vaporization of water from the skin and lungs.

¹ Guillemot: Thèse de méd., Paris, 1878.

² Bouchut: Traité de diagnostic, Paris, 1883, p. 251.

³ Lefèvre: Chaleur animale, Paris, 1911, p. 384.

The only method of heat loss that the organism can restrict to any great extent is the transportation of the blood from the interior to the surface. The other factors depend on the atmospheric conditions as found in Nature or as modified by man.

Our debts to the environment are partly paid by the constant activity of certain vital organs. Loewy¹ estimates that heart action accounts for about 3.6 per cent of the metabolism of man and the respiratory movements for about 10 per cent. Krogh² who reviews this subject considers that the kidney metabolism may be 5 per cent of the whole and that the functional activities of the various organs may total 25 per cent of the so-called resting metabolism. This is one reason why he prefers the term standard metabolism since a theoretical basal could be obtained only by stopping the heart and various other organs.

Apparently, therefore, about three-quarters of the heat produced under basal or standard conditions is derived from oxidations in resting tissues. We are not quite certain as to the tone of the skeletal muscles but are inclined to believe them responsible for a large portion of the basal metabolism. We shall see later that a complete removal of thyroid secretion from the body causes a diminution of 40 per cent of the basal figures.

Metabolism takes place within the cells. Krogh says: "In warm-blooded animals the 'environment' of the cells is maintained practically constant with regard to temperature, concentration of hydrogen ions, salts, oxygen, sugar and probably other sources of energy. The cells have lost consequently their power of adaptation to changes in all these respects, and if one of the regulating mechanisms breaks down the death of the organism results. It is only natural, therefore, that in these animals the standard metabolism is a constant which is independent of changes in the outside world, because these changes are always toned down to insignificance by the regulating mechanisms before reaching the cells."

The shape of the curve representing the level of the basal metabolism at various ages at once arouses our interest. If we compare it with the curves showing the increase in height

¹ Loewy: Oppenheimer's Handbuch der Biochem., 1913, Ergänzungs-Band.

² Krogh: Respiratory Exchange of Animals and Man, New York and London, Longmans Green & Co., 1916.

and weight at various ages, given by Benedict and Talbot, we note the periods of most rapid growth occur in the first year and at the age of puberty. In boys, growth continues slowly for several years after the age of twenty; in girls, it ceases almost completely at the age of eighteen. During childhood there is also a rapid change in the bodily proportions, as indicated by Bardeen's height-weight index.¹ At birth the liver and thyroid are relatively larger than in adult life and it is quite possible that these have some influence in determining the higher level of metabolism. In childhood the food intake is much larger in proportion to body weight, and we may be dealing with a relative over-nourishment per kilogram of substance. The possible influence of the sex glands will be discussed later. It must be remembered that we have no quantitative estimations of the secretions of the endocrine glands at different ages. The relatively small size of children accounts in part for the higher metabolism per kilogram of body weight, but the curves we are discussing show that the metabolism is increased per unit of surface also.

Brody and Ragsdale² in their study of the equivalence of age in animals have given some exceedingly interesting curves of the rate of growth of various species. One representing the velocity of growth in children is shown in Fig. 35. It will be noted that there are three cycles, the first coming in the first year when the metabolism of babies is rising rapidly, the third cycle falling at the time of puberty when there are some evidences of changing basal metabolism.

Brody³ in a further analysis of the kinetics of senescence calls attention to the similarity of the curves representing many biological phenomena such as the duration of life of aseptic flies (*Drosophila*), the milk production of cows, the egg production of fowls, and the death-rate for certain diseases of man. He has concluded that "the course of decline of vitality with age due to the process of senescence, when not complicated by the process of growth follows a simple exponential law; that is the degree of vitality or of senescence (defining vitality as the reciprocal of senescence) at any moment is, regardless of age, a constant percentage of the degree of vitality or senescence of the preceding moment.

¹ Bardeen: Carnegie Institution of Washington Publication No. 272, 1920.

² Brody and Ragsdale: Jour. Gen. Physiol., 1922, 5, 205.

³ Brody: Jour. Gen. Physiol., 1924, 6, 245.

This exponential law is the same as the law of monomolecular change in chemistry.

"During the actively growing period of life the index of vitality rises, due to the process of growth and the course

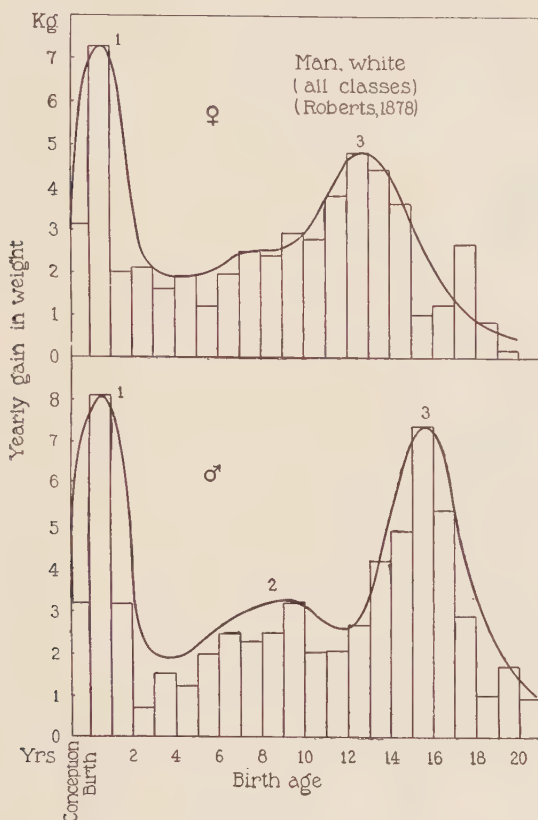


FIG. 35.—Velocity curves of growth. Ordinates represent the velocities of growth; the height of rectangles represents gains in weight for the ages shown on the abscissæ. The maxima of the first and third cycles are presented on a base-line of the same length. (Brody and Ragsdale.)

of vitality in the case when the growing period is included in the vitality curve, follows a rising and falling course. This rising and falling course may often be represented by an equation used to represent the course of accumulation and disappearance of a substance as the result of two simultaneous consecutive monomolecular chemical reactions."

Brody has applied such an equation to the variations of

basal metabolism with age as given by Du Bois in 1916. It so happens that he used the curve expressing the results in terms of Meeh's surface area formula. While the level of this is somewhat lower than those drawn according to more accurate surface formulæ the shape is almost the same.

There are many other profound changes taking place in the months just before and just after birth. The embryo and new-born baby shows a progressive gain in protoplasm and

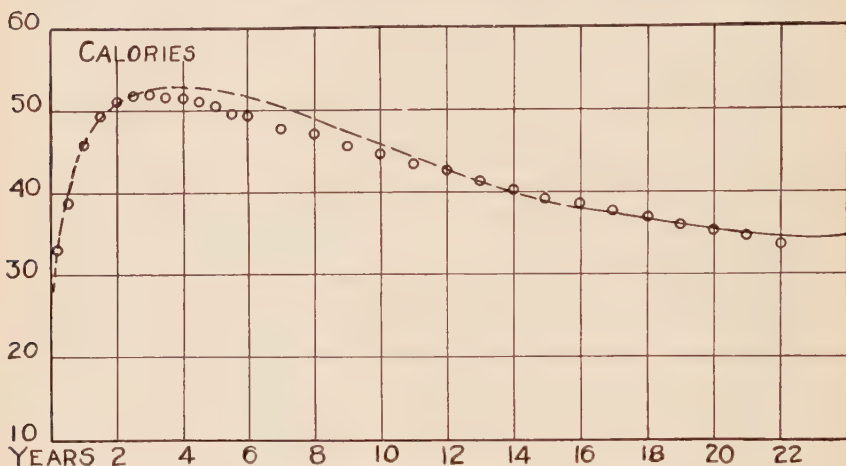


FIG. 36.—Variation of basal metabolism with age; calories per hour per square meter of body surface—Meeh's formula. Dash line shows average for males: Figure traced and legend quoted from Chart 2 of paper by Du Bois.¹

The circles represent the equations: $y = 56e^{-0.024t} - 32e^{-1.224t}$, if the intra-uterine period of growth is not considered; $y = 57.8e^{-0.024(t + 0.78)} - 83e^{-1.224(t + 0.78)}$ if the intrauterine period of growth is considered, and if it is assumed that the duration of intrauterine period of growth is 0.78 year. (Brody.)

relative loss in water. Fig. 37 taken from Armsby and Moulton² demonstrate this in young swine. As the growing organism becomes richer in nitrogen there is a compensatory diminution in the percentage of water. We should therefore naturally expect an increase in metabolism as the vitally active tissue replaces inert water.

In this connection it is interesting to compare the curves for average pulse-rate and metabolic-rate as given by Sutliff and Holt.³

¹ Du Bois, E. F.: Arch. Int. Med., 1916, 17, 887.

² Armsby, H. P., and Moulton, C. R.: The Animal as a Converter of Matter and Energy, Chemical Catalog Company, 1925.

³ Sutliff and Holt: Arch. Int. Med., 1925, 35, 224.

There are so many curves, so many factors which are roughly proportional to the basal metabolism that one is naturally confused. We must not assume that there is necessarily a connection between two phenomena just because they can be represented by similar curves.

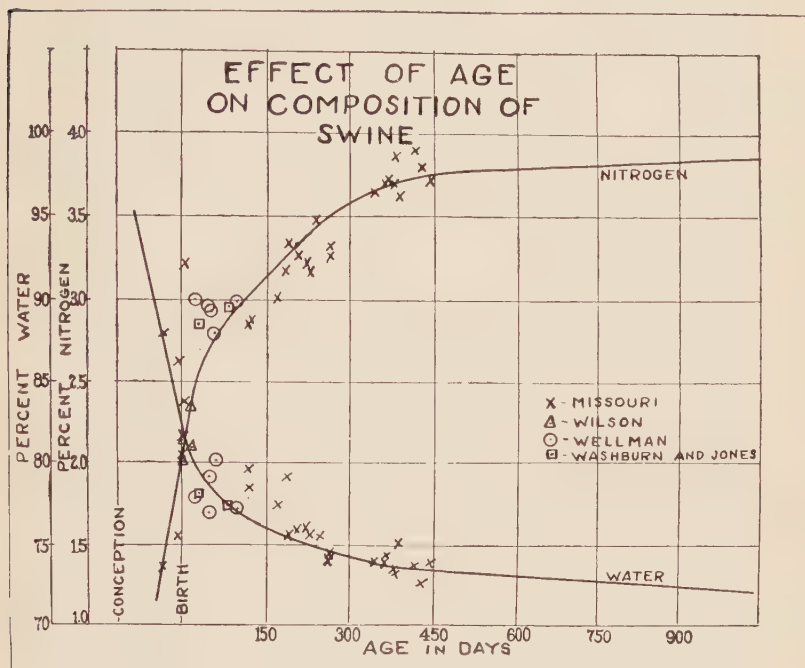


FIG. 37.—Chart showing that in young swine there is a rapid increase in the percentage of nitrogen and a corresponding decrease in the percentage of water contained in the bodies of the animals. (From Armsby and Moulton.)

Most physiologists have expressed the opinion that the higher metabolism of children is due to a specific stimulus associated with growth. Indirect evidence is furnished by the high metabolism at the age of one year and the indications of high metabolism at the time of the onset of puberty. A similar high level of metabolism occurs in the convalescence following typhoid fever.¹ Krogh² points to the low metabolism during the first few months of life as evidence against

¹ Coleman and Du Bois: Arch. Int. Med., 1914, 14, 168; Clin. Cal. 7; Ibid., 1915, 15, 887.

² Krogh: Respiratory Exchange of Animals and Man, London and New York, Longmans, Green & Co., 1916.

the stimulating effect of growth, since growth is most rapid at this period of infancy. In his opinion "the factor which is most probably responsible for the regular increase in metabolism of young children is the development of the muscular system *as such*, and perhaps simply the gradual development of a muscular tone."

The metabolism of the new-born is almost as low per unit of weight as that of an adult, and the infant during the first few days of life seems to continue at about the same metabolic

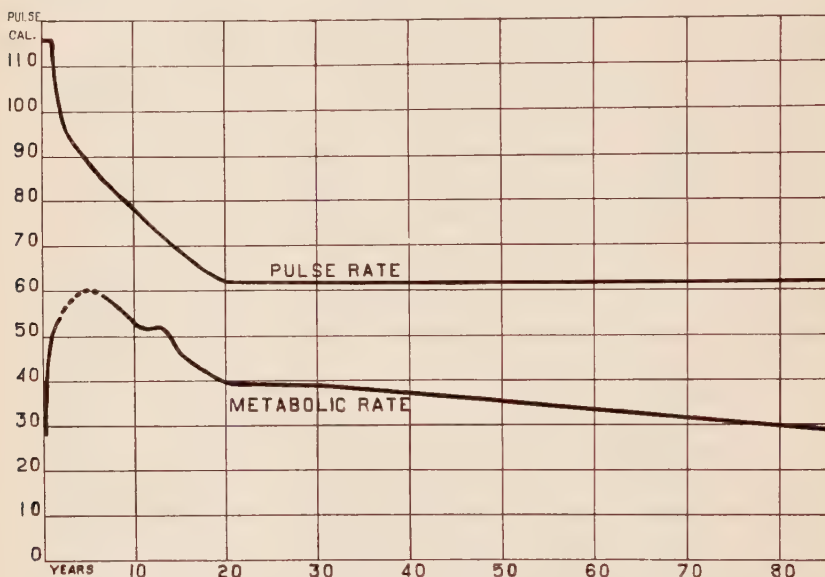


FIG. 38.—Curve of basal pulse-rate for males, aged from one to eighty years, compared to the curve of basal metabolism per square meter of body surface hourly for males. (Sutliff and Holt.)

rate as if it were still part of the mother. It takes a year before the cells have assumed the high level of metabolic activity characteristic of children who are old enough to walk. Certainly the body cells in adult life can change their rate of metabolism rather rapidly with the influence of undernutrition or thyroid extract. It is, however, quite possible that changes occur more slowly at a period when the organism is adapting itself to a new existence.

We have spoken of the body as an inert mass which loses heat to the surrounding air and have shown how a cadaver cools rather rapidly. Let us go back to the cooling of inani-

mate objects and refresh our memory of physics. Newton believed that the rate of cooling was proportional to $t - t'$, t representing the temperature of the object and t' the temperature of the surrounding medium. The heat lost per second would equal $K(t - t')$, K being a constant to be determined by experiments. This law has been found to be nearly true if the temperature deficiencies are not large. Dulong and Petit modified this slightly and gave the formula: Heat loss = $K(a^t - a^{t'})$ when K and a are constants depending on the nature and area of the surface of the body. Stephan has made a third formula which seems to apply to a much greater range than either of the others: Heat loss = $Sc[(T)^4 - (T')^4]$, S being the area of the radiating surface and c a constant depending on the nature of the surface.

There are evidently three important factors in heat loss, the temperature difference, the nature of the surface and the area of the surface. We noted on p. 155 that with mammals the heat loss shows little change even with considerable variations in the temperature of the surrounding air. The character of the surface seems to have much less effect in mammals than in the case of inanimate objects. Man can change the temperature of the surrounding air by heating his house and by clothing his body. He can change the surface by changing his clothing and can even change the character of the integument by sweating and by vasoconstriction. Physiologists have been uncertain as to the laws which will account for the effects of temperature differences and character of the surface. They have, however, found that under similar physiological conditions the basal metabolism of different mammals is roughly proportional to the surface area. The cause of this is still problematical, but while it is interesting to speculate regarding the cause it is of more importance to analyze the facts.

There is an extensive literature on this subject which is well reviewed by Lusk,¹ by Harris and Benedict² and by Murlin.³

The surface area law was demonstrated quite clearly in

¹ Lusk: *Science of Nutrition*, 3d edition, New York, 1917, p. 118; Lusk: *Jour. Am. Med. Assn.*, 1921, **77**, 250.

² Harris and Benedict: *Carnegie Institution of Washington Publication No.* 279, 1919, p. 129.

³ Murlin: *Science N. S.*, 1921, **54**, 196.

1883 by Rubner¹ and almost simultaneously by Richet² in France and physiologists, therefore, speak of Rubner's law or the law of Rubner and Richet. Before Rubner, Bergmann in 1848 had advanced such a theory and at about the same period Bidder and Schmidt and Regnault and Reiset seem to have had a very clear conception of the relationship. Before them, in 1839, Sarrus and Rameaux stated that since the loss of heat in animals must be proportional to their surface area, heat production must be proportional to the same unit. Probably a further search of the old literature would reveal that these were not the first to publish this theory.

Both Rubner and Richet showed that with animals of different size the heat production was approximately the same per square meter of body surface though it differed greatly per kilogram of body weight. Lusk³ says: "Rubner later came to a better understanding regarding the law of surface area. He found that two guinea-pigs of different sizes had the same heat production per square meter of surface even though they lived surrounded by air at a temperature of 30° C., thus excluding all thermal influences. He realized from this, that the level of the basal metabolism could not be caused by the influence of cooling on the body. Rubner,⁴ however, stated that he believed that the phenomenon observed was the result of accommodation to the action of cold to which animals in former ages had been exposed."

TABLE 41.—METABOLISM OF VARIOUS WARM-BLOODED ANIMALS.

	Weight, kg.	Calories produced.	
		Per kilo.	Per sq. m. surface.
Horse	441.00	11.3	948
Pig	128.00	19.1	1078
Man	64.30	32.1	1042
Dog	15.20	51.5	1039
Rabbit	2.30	75.1	776
Goose	3.50	66.7	969
Fowl	2.00	71.0	943
Mouse	0.018	212.0	1188
Rabbit (without ears) . .	2.30	75.1	917

¹ Rubner: *Ztschr. f. Biol.*, 1883, 19, 549.

² Richet: *La Chaleur animale*, Paris, 1889, p. 222.

³ Lusk: *Science of Nutrition*, 3d edition, 1917.

⁴ Rubner: *Die Gesetze des Energieverbrauchs bei der Ernährung*, Leipzig and Vienna, 1902, p. 174.

The above table has been assembled by Lusk from the works of Erwin Voit¹ and Rubner.² While much of the data was obtained at a time when experiments were not made under strictly basal conditions the table demonstrates the point is question. Armsby, Fries and Braman³ have recently published a similar table compiled from the best modern work.

TABLE 42.—MEAN DAILY BASAL KATABOLISM PER SQUARE METER OF BODY SURFACE.

Species.	Basal katabolism, calories.
Man (complete muscular rest), Benedict <i>et al.</i> (height-weight formula)	935 \pm 5
Women (complete muscular rest), Benedict <i>et al.</i> (height-weight formula)	886 \pm 6
Cattle (lying), Armsby <i>et al.</i> (Moulton's formulæ)	964 \pm 24
Hogs (lying, Meissl <i>et al.</i> Tangl, Fingerling <i>et al.</i> (Meeh's formula)	1078 \pm ?
Horse (standing quietly), Zuntz and Hagemann	948 \pm ?

The uniformity is rather surprising. More extensive work will doubtless disclose many species of animals where the variations are greater but we must not expect in physiology the exactness found in physical measurements of inanimate objects.

The theory of Kassowitz⁴ that the greater metabolism of small animals is due to shorter nerve paths has not received support from other physiologists.

It has long been perfectly obvious that the basal metabolism per square meter of body surface varies with age, with the state of nutrition, with disease. In fact this book is devoted to a study of the variations. It is also obvious that the basal katabolism is not caused by the temperature difference between the body and the air at any one time. If this were the case, the basal metabolism would cease to functionate in warm climates when the air temperature equalled or exceeded that of the body. This would result in the death of the cells.

We can only apply the physical laws of cooling if we conceive of a world at a uniform atmospheric temperature inhabited by warm-blooded animals with a uniform body

¹ Voit: Ztschr. f. Biol., 1901, 41, 120.

² Rubner: Energiegesetze, 1902, p. 282.

³ Armsby, Fries and Braman: Jour. Agric. Research, 1918, 13, 43.

⁴ Kassowitz: Ztschr. f. Kinderheilk, 1913, 6, 240.

temperature, with similar surface coverings living under similar physiological conditions of nourishment. In such a world the loss of heat from each animal would be proportional to its surface area. The heat production must equal the heat loss. If it were smaller than the loss the animal would cool to the temperature of the surrounding medium. If the heat production were greater than the loss the animal would become warmer and warmer and finally burn up.

At some stage in the development of the world there must have been a differentiation of the various species of warm-blooded animals and a fixation of such physiological levels as body temperature, blood chlorides, hydrogen-ion concentration and basal metabolism. This might have occurred in a locality or period when the temperature was uniform or else when the variations in temperature balanced each other so as to produce the same effect as uniformity.

It is believed by many that the metabolism is proportional to the surface area because of some more fundamental factor which is itself proportional to surface area. Carl Voit, for instance, held that the mass of the cells and their power to oxidize materials determine the height of metabolism. This theory can perhaps be brought into harmony with the facts regarding surface area through the work of Dreyer, Ray and Walker¹ and of Moulton.² The British investigators have found that the blood volume, cross-section of the aorta and the trachea are all proportional to the body surface in warm-blooded animals and that the surface is proportional to the weight raised to the 0.70 to 0.72 power. Moulton and his collaborators have made extensive analyses of the composition of beef cattle and have found the relationships given in Table 43.

TABLE 43.—RELATIONSHIPS OF COMPOSITION OF BEEF CATTLE (MOULTON).

Fat animals	Surface area = $0.158 W^{\frac{5}{9}}$
	W = warm empty weight.
Other animals	Surface area = $0.1186 W^{\frac{5}{9}}$
All animals	Surface area = $0.1034 (W_1)^{\frac{2}{3}}$
	W_1 = fat-free empty weight.
Surface area is proportional to $N^{\frac{2}{3}}$	N = total body nitrogen in kg.
Surface area is proportional to $0.8 B^{\frac{5}{9}}$	B = total blood weight in kg.

¹ Dreyer, Ray and Walker: Proc. Roy. Soc., 1912-1913, 86, 39, 56.

² Moulton: Jour. Biol. Chem., 1916, 24, 299.

Peabody and Wentworth¹ found a close agreement between vital capacity and surface area. Dreyer² says that there can be no question that the most accurate manner in which to express the vital capacity is as a function of the body surface by means of the formula $\frac{W^n}{\bar{V} \cdot \bar{C}} = K$ when n is approximately $\frac{2}{3}$ or more accurately 0.72. West³ clearly proves the same point, showing that in a large series of measurements the results were quite uniform according to surface area, 71 per cent of the individuals coming within 10 per cent of the averages (2.61 L per sq. m. for men, 2.07 L for women).

Von Pirquet⁴ believes that the metabolism is proportional to the surface area of the intestine but since this is ten times as long as the sitting height and its breadth about $\frac{1}{100}$ its length, the surface of the intestine about equals the square of the sitting height. He also states that the surface area of the intestines equals the $\frac{2}{3}$ power of ten times the weight in grams.

We see, therefore, that there are many components of the human body proportional or nearly proportional to the surface area. Some of these may show this relationship because they are affected by the metabolism and need of the body for oxygen. Some one of these factors may be the determining cause of the level of the basal metabolism.

We shall await with particular interest further studies on the basal metabolism of small mammals studied under the most rigid precautions to exclude variations in all the factors mentioned in Chapter VII. Such respiration experiments should be accompanied by actual measurements of the surface area of the animals and analyses of their bodies to determine the total nitrogen and if possible the weights of the various organs. If some mammals can be found which show a great disproportion between the surface area and protoplasmic mass this will give a clue as to which has the greater influence on basal metabolism. I am inclined to believe that there will be rather large differences between certain wild and domestic animals depending on muscular development and habits of life. Perhaps we should compare in one series college athletes,

¹ Peabody and Wentworth: *Arch. Int. Med.*, 1917, **20**, 443.

² Dreyer: *Lancet*, 1919, **197**, 227.

³ West: *Arch. Int. Med.*, 1920, **25**, 306.

⁴ Von Pirquet: *System der Ernährung*, Berlin (Springer), 1917.

race horses, fox hounds, hares and weasels, in another series barbers, pet ponies, poodles, guinea-pigs and white mice.

Terroine¹ in a recent book has given some analyses of the nitrogen content of small mammals and birds which indicate that in these species the protoplasmic mass is proportional to weight rather than to surface. Respiration experiments were not made but we may hope that this gap will be filled.

Physiologists seem to have spoken of protoplasmic mass and its relationship to surface area without having made any careful analysis of the figures on hand. This has been pointed out by Carman and Mitchell² who measured the surfaces of sixty-two rats, finding that the surface area of a 200-gram animal to be only 389 square centimeters. They speak of the older belief that surface area controlled basal metabolism on account of its relationship to heat loss, and when they come to the discussion of the more recent belief that surface area is related to the body's content of protoplasm, they say: "In giving this interpretation to the surface area law, it becomes entirely empirical in nature, while its application to different species of animals differing widely in size implies a difference in anatomical composition so wide as to be absurd. For example a man of average height (173 cm.) and weight (70 kilograms) weighs 350 times as much as a 200-gram rat, although his surface area is only forty-seven times that of the rat. According to this latest interpretation of the surface area law, the man should contain only 9.4 kilograms (0.2×47) or 13.4 per cent of protoplasmic material, on the extreme assumption that the rat consists entirely of active cellular tissue. In its application to different species of animals, at least, it appears that the literal interpretation of the law, if such it proves to be, is the more plausible of the two."

It is difficult to reconcile any causal relationship between surface area and basal metabolism with the fact that animals and men show practically no change in heat production when exposed to a rather large range of environmental temperatures. This may be due to the mechanism described by Barr and Du Bois in their study of malarial chills. They suggested that the body could restrict heat elimination by vasoconstriction in the skin and subcutaneous tissues so

¹ Terroine and Zunz: *Le Metabolisme de Base*, Les Presses Universitaires de France, 1925.

² Carman and Mitchell: *Am. Jour. Physiol.*, 1926, **76**, 380.

that the circulating blood was cooled deep under the surface instead of in the skin. It is quite possible that the physiological exterior of the circulating blood is kept at the same temperature when the atmosphere is cooled by means of such a vasoconstriction which changes the skin into a "suit of clothes." Barbour¹ and his associates have been studying certain changes in the water content of blood and skin which may aid in this process.

There has been a great deal of argument as to the validity of the surface area law as applied to man. Since it had been

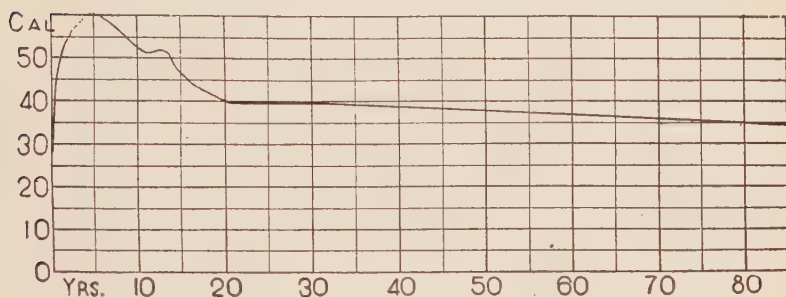


FIG. 39.—Curve showing the average calories per square meter per hour produced by males of different ages according to the estimations of Aub and Du Bois. The curve is probably too high between the ages of one and fifteen years.

adopted by Rubner and most of the other German physiologists it was very naturally used as a standard of measurement by Lusk and his pupils in America. Thus McCrudden and Lusk² employed it in 1913 when they studied a dwarf and Coleman and Du Bois³ used it in obtaining a normal standard with which to compare their typhoid patients in 1914. The Sage investigators recalculated the results of various series of normal controls according to the new surface area formulas and published curves in 1916.⁴

As a result of studies on old men Aub and Du Bois⁵ published the curve shown in Fig. 39 and in order to express the matter

¹ Barbour: *Am. Jour. Physiol.*, 1924, **67**, 366, 378, 388, 399; 1925, **73**, 315, 321, 665; **74**, 204.

² McCrudden and Lusk: *Jour. Biol. Chem.*, 1913, **13**, 447.

³ Coleman and Du Bois: *Arch. Int. Med.*, 1914, **14**, 168.

⁴ Du Bois: *Clin. Cal. 12. Arch. Int. Med.*, 1916, **17**, 887; *Am. Jour. Med. Sci.*, 1916, **151**, 781.

⁵ Aub and Du Bois: *Clin. Cal. 19. Arch. Int. Med.*, 1917, **19**, 823.

concisely published a brief table (Table 44). This table gives the results in steps for each ten-year period and Aub and Du Bois have been criticized by Harris and Benedict, Boothby and Sandiford, Krogh and a half a dozen others for not making a smooth curve. These authors have evidently missed the smooth curve published on the second page of the article and also given by Lusk in his book.¹ Both the curve and the table are based on the hypothesis that metabolism is proportional to the surface area but changes with age and is lower in women.

TABLE 44.—SO-CALLED SAGE NORMAL STANDARDS. (AUB AND DU BOIS.)
CALORIES PER SQUARE METER OF BODY SURFACE PER HOUR (HEIGHT-
WEIGHT FORMULA.)

Age, years.	Males.	Females.
14 to 16	46.0	43.0
16 to 18	43.0	40.0
18 to 20	41.0	38.0
20 to 30	39.5	37.0
30 to 40	39.5	36.5
40 to 50	38.5	36.0
50 to 60	37.5	35.0
60 to 70	36.5	34.0
70 to 80	35.5	33.0

A great deal of light has been thrown on the "surface area law" by its chief opponent, Dr. F. G. Benedict, of the Nutrition Laboratory in Boston. At the end of the first monograph on the metabolism of infants, Benedict and Talbot² state that it is reasonable to suppose that the active mass of protoplasmic tissue may develop normally on the ratio of the two-thirds power of the weight which is the same ratio as that of the surface area. They conclude: "The basal metabolism, as we have outlined above, cannot in any wise be considered a direct function of the body weight and the body surface, and particularly has no relationship with body surface on the basis of the law of cooling bodies. We believe that our evidence points strongly and conclusively to the fact that the active mass of protoplasmic tissue determines the fundamental metabolism. The absence as yet of a direct mathematical measure of the proportion of active protoplasmic

¹ Lusk: Science of Nutrition, 3d edition, p. 128.

² Benedict and Talbot: Carnegie Institution of Washington Publication No. 201, 1914, p. 168.

tissue does not, we believe in any wise affect the convincing nature of our evidence." Writing again in 1920¹ they say:

"Our present position on this point can be no better set forth than by repetition of an opinion expressed six years ago to the effect that we believe body surface has no significance in connection with heat production, except that it represents a general morphological law of growth."

Benedict² in several publications has raised objections to the popular conception of the surface area and with Harris³ has made an extensive critique of the body surface law. Benedict's objections to the use of the surface area as a standard seem to be three-fold. First, he objects to an "erroneous conception" as to the existence of a causal relationship between surface area and heat elimination. Second, he shows that metabolism is not proportional to surface area if we compare adults and infants and well-nourished men with those who are starving. Finally, he points out the differences found in the basal metabolism of homogeneous groups when the surface area is used as a standard.

As to the first objection, it is doubtful if many physiologists have held the belief that the surface area was the *immediate* cause of the metabolism. If they did hold an erroneous belief as to the causal relationship this would not in any way change the practical application of the figures. For instance, women would continue to menstruate every twenty-eight days even if physiologists believed that this was caused by the changes in the moon.

The second objection that the surface area law will not hold with children and starving men has little bearing on the present discussion. Rubner clearly showed that the law was applicable only under similar physiological conditions. The third objection as to the extent of the variations is, as Harris and Benedict point out, largely a matter of personal opinion. If the surface area is the best practical standard we should adopt it until a better is found.

According to elaborate statistical studies of Harris and Benedict⁴ on a large series of normal subjects the metabolism

¹ Benedict and Talbot: Carnegie Institution of Washington Publication No. 302, 1921, p. 63.

² Benedict: Jour. Biol. Chem., 1915, 20, 263; Am. Jour. Physiol., 1916, 41, 292.

³ Harris and Benedict: Carnegie Institution of Washington Publication No. 279, 1919; Scientific Monthly, 1919, 8, 386; Jour. Biol. Chem., 1921, 46, 257.

⁴ Harris and Benedict: Carnegie Institution of Washington Publication No. 279, 1919.

on the whole is more nearly proportional to surface area than to weight and more nearly proportional to the surface as measured by the new height-weight formula than if measured by the less accurate formula of Meeh. Some of the calculations, however, show but little difference between weight and surface. The reason for this lack of difference is explained as follows by Murlin:¹ "Suppose, for example, we have two infants weighing 7 and 8 kilograms respectively. Expressing their weights in grams and their surfaces in square centimeters by the Meeh and Lissauer formulæ, we have the proportions shown in the first line of Table 45. The ratio of weights in 0.88 : 1 and of surfaces 0.91 : 1. Now it is obvious that if the metabolism of these two children is proportional to their weights it must of necessity also be nearly proportional to surface. With two youths weighing 40 and 41 kilograms the surfaces bear to each other exactly the same ratio as the weights, whether the Meeh or Lissauer formula be employed. Both, therefore, will be equally good measures of metabolism for the two individuals. The 'discovery' that surface is no better as a measure of metabolism, than weight *as between individuals of nearly the same weight* could, therefore, have been made with paper and pencil."

TABLE 45.—RELATION OF BODY WEIGHTS AND SURFACES TO EACH OTHER (FROM MURLIN.)

Weight.	Ratio.	Meeh-Rubner $11.93\sqrt{(W)^2}$.	
		Surface, sq. m.	Ratio.
7.0	0.4354	
8.0	0.88	0.4760	0.91
20.0	0.8768	
21.0	0.95	0.9058	0.97
40.0	1.3920	
41.0	0.98	1.4150	0.98+
4.0	0.2990	
40.0	0.10	1.3920	0.210
3.5	0.2740	
70.0	0.05	2.0210	0.135

Bearing this criticism in mind, let us turn to the large group of men between the ages of twenty and thirty-nine years studied by Harris and Benedict and apply the method used by Gephart and Du Bois. The mean of all the men can be calculated from p. 118 of their publication. We can then select groups of tall, short, heavy, light, overweight and underweight men and compare then in Table 46. The results

¹ Murlin: Science, 1921, 54, 196.

show a much smaller variation from the average in the case of surface area than body weight. Benedict¹ shows that per square meter of body surface the average metabolism of men is level with increasing weights but qualifies this as follows: "While the straight line which is at a constant level in the case of men where the heat per square meter is referred to weight would seem to be an admission of the constancy of heat production per square meter of body surface with men, we believe that no one inspecting this chart, with its wide scatter of individual points, can conclude that this line, which represents trend only, can be logically looked upon as a demonstration of the general thesis that the heat production per square meter of body surface with man is constant. With women it would seem as if a slight slant to the line more closely fitted the general trend, but here again, owing to the wide scatter of the points, there is no evidence of regularity in the relationship between heat production and surface area."

TABLE 46.—METABOLISM OF VARIOUS GROUPS OF MEN BETWEEN AGES OF TWENTY AND THIRTY-NINE YEARS TAKEN FROM NORMAL SUBJECTS OF HARRIS AND BENEDICT.

Number of subjects.		Calories per kg., per day.	Percentage deviation from mean.	Calories per sq. m., per day.	Calories per sq. m., per hour.	Percentage deviation from mean.
114	Mean of all between 20 and 39 years	25.79	..	928.7	38.7	
11	Over 181 cm. Taller than 90 per cent of men	25.44	- 1.4	913.9	38.1	-1.6
8	Under 163.5 cm. Shorter than 90 per cent of men	27.96	+ 8.4	942.5	39.3	+1.5
3	Over 78.5 kg. Heavier than 90 per cent of men	20.50	-25.0	880.0	36.7	-5.3
26	Under 57.5 kg. Lighter than 90 per cent of men	27.69	+ 7.4	917.4	38.2	-1.2
5	More than 15 per cent overweight for height	22.54	-12.6	946.2	39.4	+1.9
27	More than 15 per cent underweight for height	26.97	+ 4.6	891.9	37.1	-4.0
	Mean deviation from mean of all 114	..	9.9	2.6

It is true that the scatter of dots seems great since they occupy the whole chart. We must remember that no base

¹ Benedict and Talbot: Carnegie Institution of Washington Publication No. 302, 1921, pp. 182 and 183 (Figs. 54 and 55).

line is given and that each chart represents a range of about 20 per cent above and below the average.

Dreyer¹ also has made a statistical study of the normal controls reported by Magnus-Levy, the Nutrition Laboratory in Boston and the Russell Sage Institute of Pathology in New York. As a result he has evolved the following formula to

express the normal metabolism;
$$\frac{W^N}{C \times A^{0.1333}} = K ; W = \text{net body weight in grams, } C = \text{total calories produced in hours, } A = \text{age in years. } K = 0.1015 \text{ in males and } 0.1127 \text{ in females.}$$
 This he finds expresses the basal metabolism in an extremely satisfactory manner over a wide range of body size and age and indicates that basal metabolism is not a simple function of the body surface. It is obvious that Murlin's criticism applies to this formula just as it does to the Harris-Benedict.

Finally, the best confirmation of the statement that metabolism is proportional to surface area lies in the multiple prediction table of Harris and Benedict. By purely statistical methods they found that the formula which would predict the metabolism of the individuals of their series most closely were as follows:

For men

$$h = + 66.4730 + 13.7516w + 5.0033s - 6.7550a$$

For women

$$h = +655.0955 + 9.5634w + 1.8496s - 4.6756a$$

where h = total heat production per twenty-four hours, w = weight in kilograms, s = stature in centimeters and a = age in years.

It will be noted that the factors of height and weight are used and also a correction for age. Boothby and Sandiford² Means and Woodwell³ and many others have found that the results from this calculation parallel closely the surface area calculations. The reason for this becomes apparent if we plot the Harris-Benedict prediction formula on the same chart as the height-weight surface area. This can be done for any age and the largest age group, namely, men of thirty, was

¹ Dreyer: *Lancet*, 1920, **2**, 289.

² Boothby and Sandiford: *Basal Metabolic Rate Determinations*, Philadelphia and London, W. B. Saunders & Co., 1920, p. 15.

³ Means and Woodwell: *Arch. Int. Med.*, 1921, **27**, 608.

selected¹ (Fig. 40). The results in calories per hour for the two methods were plotted together and found to be almost parallel. They would practically coincide if a standard percentage were added to the Harris-Benedict figures or subtracted from those of the Sage investigators. The similarity is not as great in some of the other age groups but it is sufficient to indicate that the Harris-Benedict formula could be used to predict surface areas. In fact, Boothby and

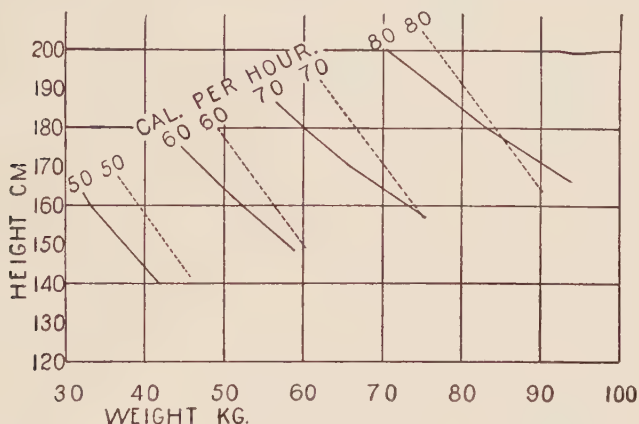


FIG. 40.—A comparison of the normal standards for men thirty years of age. The solid curved lines give the calories per hour according to the surface area chart and standards of Aub and Du Bois. The dotted lines represent the figures according to the Harris-Benedict multiple prediction tables. For instance, a man thirty years of age, 180 cm. tall and 60 kg. in weight would have a predicted normal basal metabolism of 70 calories per hour according to the surface area curves, and about 67 calories per hour by the other method. The results according to the Harris-Benedict formula are lower, but the two sets of lines are almost parallel for this age group.

Sandiford² have independently demonstrated the same point in a much more convincing fashion. They have actually transformed the Harris-Benedict multiple prediction formula into a method for determining surface area and have shown that it is nearly as good for adults as the Sage height-weight formula. They have also pointed out certain discrepancies in the Harris-Benedict standards for metabolism which do not seem to be in accord with general biological principles. They say: "Harris and Benedict, in their correlation formula,

¹ Du Bois: Jour. Am. Med. Assn., 1921, 77, 352.

² Boothby and Sandiford: Jour. Biol. Chem., 1922, 54, 767.

assume that a small subject will show more than twice the percentage decrease in heat production for advancing age than a large subject, while Dr. Du Bois assumes that age affects alike both small and large people. Harris and Benedict assume a reversed action for sex depending on the size of the subject, by predicting first, that large men have a greater heat production than similar-sized women and second, that small women have a greater heat production than small men."

Krogh¹ says: "It must be admitted that the Du Bois way of introducing the age factor is in much better agreement with biological principles than the Harris-Benedict formula." He concludes as follows: "The Harris-Benedict prediction tables for the 'basal' metabolism are very reliable for average subjects but, owing to their statistical nature, less so for persons of exceptional build or higher age. The Du Bois method and table for computing the basal metabolism give results which are on an average too high (about 4 per cent or more) but they are less likely to fail when used on exceptional subjects." This seems to be a very fair summary of the whole discussion.

Fortunately the differences of opinion concerning the theories of basal metabolism do not seriously affect its practical applications. We therefore turn to a consideration of the results obtained in various diseases bearing in mind the fact that Nature has performed many beautiful clinical experiments which can throw light on the normal physiology.

¹ Krogh: Boston Med. and Surg. Jour., 1923, 189, 313.

PART II.

METABOLISM IN DISEASE.

CHAPTER X.

UNDERNUTRITION.

THE factor of undernutrition enters into almost all of our clinical problems. There are few diseases in which the diet at some time or other is not restricted, either voluntarily by the patient or intentionally by the physician. The resulting diminution of metabolism may therefore augment a similar tendency in the disease itself or may partially neutralize a tendency toward increased metabolism. As a matter of fact, many of the disputes in this field of research have arisen from an incomplete differentiation of the two factors.

In our hospital wards complete starvation may be found in diabetes, comatose or psychopathic patients, cases of obstruction of the gastro-intestinal tract, gastric ulcer and in postoperative conditions. As a rule the physician attempts to give some food. Lesser grades of undernutrition are found in a large variety of conditions such as fever, cardiorenal disease, carcinoma, etc. The clinician deliberately attempts to produce undernutrition in the obese and in many diabetics. In certain other conditions, such as fever or hyperthyroidism, he may unconsciously produce a relative undernutrition by giving a normal diet to a patient in whom disease has raised the energy requirement far above the normal.

The most important phenomenon of undernutrition is the striking reduction in the metabolism and this was recognized at an early date by the many investigators who studied professional fasters. Other physiological processes are affected also and some of these are of considerable importance in the study of disease. From the voluminous books on this subject it is necessary to select the findings which will be of greatest service in clinical medicine and in the solution of the problems of metabolism.

Literature on Starvation.—The changes in the bodily processes which accompany complete starvation have been thoroughly discussed by Lusk,¹ Benedict² and Morgulis.³ For the sake of brevity it is necessary to omit the extremely interesting work that has been done on the lower animals and concentrate our attention on the human subjects. The professional fasters, Cetti and Breithaupt, were studied in 1887⁴ and Cetti was again studied by Luciani⁵ the next year and on many subsequent occasions by other investigators. Brugsch and his associates⁶ paid special attention to the excretion of ketones, Cathcart⁷ paid particular attention to the mineral excretion, creatin and creatinine and Benedict⁸ in 1907 added some important observations on the length of time required to deplete the stores of glycogen. Gamble, Talbot, and their associates^{9,10,11,12} have studied fasting epileptic children and Takahira¹³ has published in Japanese an unusually careful study of the metabolism of five men followed through fasting and the important period of recovery.

Benedict's Subject, Levanzin.—By far the best and most complete study of prolonged starvation was made by Benedict and his associates of the Nutrition Laboratory of Boston in 1912.¹⁴ Their subject was Mr. A. Levanzin, a native of Malta, aged forty years, who had made several previous fasts. From April 10, 1912 to April 13, the observations were made while he was on a normal diet. The fast began on April 14 and continued thirty-one days, during which time he received nothing

¹ Lusk: Science of Nutrition, third edition, Philadelphia and London, W. B. Saunders Company, 1917; Physiological Rev., 1921, 1, 523.

² Benedict: Carnegie Institution of Washington Publication No. 77, 1907; Publication No. 203, 1915; Publication No. 280, 1919.

³ Morgulis: Fasting and Undernutrition, New York, E. P. Dutton & Co., 1923.

⁴ Lehmann, Mueller, Munk, Senator and Zuntz: Arch. f. path. Anat. u. Physiol., u. f. klin. Med., 1893, 131, Suppl. 1.

⁵ Luciani: Fisiologia del digiuno; studi sull'uomo, Florence, 1889; translation of Luciani by M. C. Fraenkel, Das Hungern, Hamburg and Leipzig, 1890.

⁶ Brugsch and Hirsch: Ztschr. f. exp. Path. u. Therap., 1906, 3, 638.

⁷ Cathcart: Biochem. Ztschr., 1907, 6, 109; Jour. Physiol., 1907, 35, 500; Cathcart and Fawsitt: Jour. Physiol., 1907, 36, 27.

⁸ Benedict: Carnegie Institution of Washington Publication No. 77, 1907.

⁹ Gamble, Ross and Tisdale: Jour. Biol. Chem., 1923, 57, 633.

¹⁰ Talbot, Shaw and Moriarty: Jour. Am. Med. Assn., 1924, 83, 91.

¹¹ Shaw and Moriarty: Am. Jour. Dis. Child., 1924, 28, 553.

¹² Hoeffel and Moriarty: Ibid., 1924, 28, 16.

¹³ Takahira: Report of the Metabolic Laboratory, The Imperial Gov. Institute for Nutrition, Tokyo, January, 1925, 1, No. 1.

¹⁴ Benedict: Carnegie Institution of Washington Publication No. 203, 1915.

but distilled water. He spent his nights sleeping in the bed calorimeter while his days were occupied with respiration

[NUTRITION LABORATORY OF THE CARNEGIE INSTITUTION OF WASHINGTON, BOSTON, MASSACHUSETTS]
METABOLISM CHART OF A MAN FASTING 31 DAYS
APRIL 14 - MAY 15, 1912

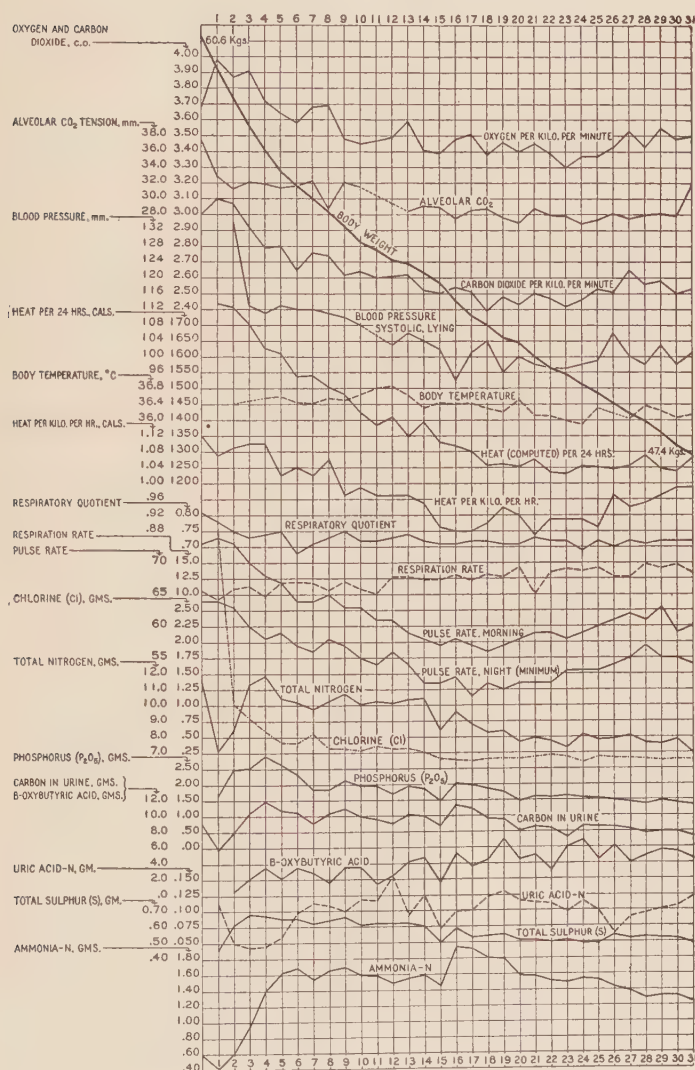


FIG. 41.—Benedict's subject, Levanzin.

experiments on the Benedict "Universal Apparatus," physical measurements, psychological tests, etc. The laboratory staff

kept him in good spirits by taking his photograph at frequent intervals. As the fast progressed, he naturally grew weaker and irritable but he did not suffer from hunger and his general condition was good. Unfortunately, at the end of the stated period he insisted on breaking the fast by taking lemons, oranges, honey and grape juice. This caused severe gastrointestinal disturbances which made it impossible to study the important period of re-alimentation.

The body temperature showed surprisingly little change from the normal and during the last ten days of the fast was only 0.2° to 0.4° C. lower than at the start. The average sleeping pulse-rate which ranged between 64 and 76 had dropped gradually to 55 on the tenth day and to 49 on the seventeenth day. Subsequently it rose slowly until it reached about 55. The blood elements showed practically no change.

Body Weight.—The loss in body weight was naturally great. From an original weight of 64.60 kilograms, there was a sharp fall to 54.1 kilograms on the tenth day. After that, the rate of loss was somewhat more gradual following a straight line curve and averaging about 320 grams a day. On the thirty-first day, the weight was 47.39 kilograms, showing a total loss of 13.25 kilograms or 21.9 per cent of the original body mass. Benedict has arranged in tabular form the weight losses of a number of professional fasters. On the fourteenth day the average weight loss was 12.6 per cent of the original figure, on the twentieth day, 15.6 per cent, thirtieth day, 20.6 per cent. Succi, on the fortieth day had lost 25.3 per cent. Dogs have suffered much greater losses. Hawk's¹ dog received nothing but water for one hundred and seven days and lost 62.9 per cent of the original weight. In the case of Levazin, Benedict calculates that the water vaporized from the skin and lungs averaged 850 to 977 grams a day in the earlier part of the fast and dropped to 300 to 400 grams after the thirteenth day. Adding this water of vaporization to the urine volume he obtained the total water eliminated. During the early part of the fast this exceeded the water consumed by 400 to 600 grams daily. After the sixth day, the excess was almost always under 300 grams and was often under 100 grams. As a matter of fact, it was calculated that the breaking down of fatty tissue and flesh after the sixth day of the fast furnished more than this excess of water so that

¹ Howe, Mattill and Hawk: Jour. Biol. and Chem., 1912, **11**, 103.

there was an actual retention of preformed water in the tissues. This seldom exceeded 150 grams a day and was not at all comparable to the edema found in fasting diabetics or in some of the starving populations of European countries.

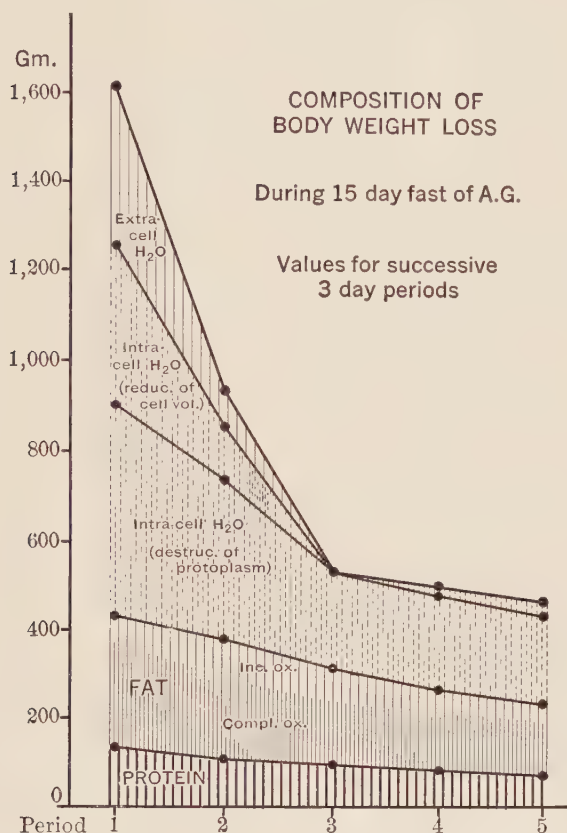


FIG. 42.—Composition of the body-weight loss of the fasting epileptic child A. G. studied by Gamble. The weight loss directly measured was 3920 grams, as calculated from the excretion of fixed bases 3986 grams.

Stored Carbohydrate.—We have seen that the loss in body weight during the early part of the fast was in part due to losses in water. Gamble, Ross and Tisdall¹ in their study of the fixed bases of fasting epileptic children have been able to show that body water is lost not only on account of the destruction of protoplasm but also, in the early part of the

¹ Gamble, Ross and Tisdall: Jour. Biol. Chem., 1923, 57, 633.

fast, on account of a reduction of tissue glycogen causing a decrease in cell volume. In Benedict's subject, as in all others, there were large losses in the glycogen stored in the liver and muscles. On the first day the respiratory quotient showed that 69 grams of glycogen had been consumed, on the second and third days about 40 grams per day, after that about 4 grams a day until carbohydrate combustion ceased on the thirteenth day. The body lost 40 to 60 grams of protein daily and 108 to 140 grams of fat. Levanzin excreted 11.5 grams of nitrogen in the urine on the day before his fast. There was as usual a fall during the first two days of the fast and he excreted 7 to 8 grams per day. When the glycogen stores became low on the third day the nitrogen rose to between 10 and 11 grams and continued at this level until the fifteenth day after which point it continued about 7 to 8 grams. This represents a higher protein metabolism than is usually found in prolonged fasting. Succi, after fifteen days of fasting, usually excreted less than 5 grams of nitrogen daily. There was, of course, in Levanzin's case no approach to the premortal rise in protein metabolism. He could probably have fasted several weeks longer before the appearance of this phenomenon.

TABLE 47.

Animal.	Weight, kg.	Percentage of calories from protein.
Pig	115.0	7.3
Man	63.7	15.6
Dog I	28.6	13.2
Dog II	18.7	10.7
Dog III	7.2	13.5
Rabbit	2.7	16.5
Goose	3.3	7.4
Fowl	2.1	10.0
Guinea-pig	0.6	10.8

Between the fourth and thirteenth days about 1 to 4 per cent of the calories were derived from stored carbohydrate. After that all came from fat and protein, the latter furnishing between 14 and 19 per cent of the total. This again is rather higher than the usual percentage and Lusk¹ gives a table which shows that in various animals, pigs, dogs, rabbits, guinea-pigs, fowls, geese and man, the percentage of calories furnished by protein in starvation is between 7.3 and 16.5

¹ Lusk: Science of Nutrition, third edition, 1917, p. 86.

per cent. This means that the smaller animals lose much more protein per kilogram of body weight than the larger animals but that per unit of body surface the figures are close together. Eighty to 90 per cent of the calories are furnished by fat until the fat stores are depleted, then the protein is consumed in greater and greater proportions until death ensues.

We must not get the idea that the various body tissues are merely burned like fuel in a stove. As they are broken down in the preliminary processes of metabolism they become available for syntheses in much the same manner as ingested food. After a few days of starvation the oxidation of glycogen is no longer apparent in most respiration experiments, Takahira's high respiratory quotients being the exception. The glycogen store is by no means depleted since it has been found in the livers of animals after many days of fasting. Extraordinarily severe measures are necessary to rid an animal of glycogen and the modern experimenters have to resort to fasting, phlorhizin and strychnine convulsions. The protein cleavage is a continued source of glucose and this may be oxidized or partially used for storage or perhaps temporarily transformed into fat. The amino-acids derived from the breaking down of the protein of one organ may be used for the regeneration of another. It has long been known that the salmon, during the spawning season, fasts for many days, yet in spite of great muscular activity deposits a large amount of new tissue in the reproductive glands.^{1, 2} There is also a selective action in the tissues from which the fat and protein are withdrawn, the muscles and glandular organs suffer most, the skeleton and nervous system, least. It would be interesting to watch rapidly growing tumors during complete starvation.

Basal Metabolism.—Perhaps the most striking feature of Benedict's experiment was the reduction in the basal metabolism. This was measured during the whole night while Levanzin was sleeping in the bed calorimeter and both the direct and indirect methods of calculation were used. Unfortunately, the direct method seems to have given results 10

¹ Miescher: *Histochemische und physiologische Arbeiten*, Leipzig, 1897.

² Paton, D. Noël: *Report of Investigations on the Life History of the Salmon in Fresh Water*, Fishery Board of Scotland, Glasgow, 1898; also *Jour. Physiol.*, 1898, 22, 333.

to 15 per cent higher than the indirect, but we are certainly not far from the correct figures for the minimal metabolism if we take the average of the two. In the daytime indirect measurements only were made, using a "universal respiration apparatus." On the first day, the basal metabolism was 1432 calories for twenty-four hours (average of direct and indirect measurements in the bed calorimeter). By the twenty-first day this had reached the lowest level of 1002 calories, rising somewhat after this and reaching 1072 calories on the last day of the fast. Benedict,¹ basing his calculations on the direct calorimetry, found the calories per kilogram of body weight per hour, 1.07 on the first day, 0.87 on the twenty-first and 0.99 on the thirty-first days. In a later publication he recalculates the results according to his photographic method of measuring the surface area which gives figures close to those obtained by the Sage height-weight method. On the first day, Levanzin produced 904 calories per square meter per twenty-four hours, on the twenty-first day, 664 calories, on the last day, 737 calories. Thus, we see that by the twenty-first day the metabolism produced 30 per cent less heat than at the start, the average kilogram of body weight produced 19 per cent less and each square meter of body surface eliminated 26 per cent less heat. During this period he had lost 16.7 per cent of his body weight. Lusk,² using Rubner's calculations estimates that Levanzin's body contained about 1788 grams of nitrogen at the beginning of the fast. By the twenty-first day he had lost 200 grams of nitrogen or 11.2 per cent of the original amount. It is evident that the fall in metabolism was caused not only by the decreased body and protoplasmic mass but also by some specific and unknown factor which tends to protect the organism from the evil results of starvation.

Ketosis in Starvation.—It has long been known that in man starvation is accompanied by an excretion of ketone bodies in the urine. This ketosis seems to be exactly the same as that which is found in diabetes. It makes its appearance as soon as the glycogen stores of the body are diminished to such a point that the carbohydrate metabolism falls below the level necessary for the complete combustion of the fatty acids. In the case of Levanzin, the total hydroxybutyric acid was 0.5

¹ Benedict: *Am. Jour. Physiol.*, 1916, 41, 292.

² Lusk: *Science of Nutrition*, third edition, 1917, p. 95.

grams on the second day of the fast, 2.1 grams on the third day and after that fluctuated between 1.4 and 7.0 grams per day. With the resumption of food, the amount fell promptly to below 1 gram. Shaffer¹ has carefully calculated the ketogenic-antiketogenic ratios of the stores metabolized by Levanzin and has shown that the ketosis appeared when more than one molecule of fatty acid was oxidized for each molecule of glucose. He has found that this occurs in normal men and in diabetics when the respiratory quotient falls below 0.76. Wilson, Levine, and Rivkin² have shown that fasting children develop a ketosis with a higher respiratory quotient than in the case of adults. This will be discussed later in the chapter on Diabetes. The sudden diminution in ketosis when food was taken at the end of the fast is coincident with a rise in the respiratory quotient above 0.76. This ketosis of Levanzin's was noticeably less than that found by Brugsch³ with Succi and by Grafe⁴ with his fasting woman. The former obtained from 8.4 to 13.6 grams of hydroxybutyric acid between the twenty-third and thirtieth days of starvation. The latter reports 15 to 16 grams of acetone bodies in the third week of starvation. The extent of ketosis is probably determined by the relationship between the carbohydrate derived from the protein and the total fat metabolism. There does not seem to be any serious danger from this ketosis of starvation under ordinary conditions. If, however, the starvation is the accompaniment of some disease which either increases the total metabolism or renders the patient more susceptible to the effects of the ketones the results may be disastrous. It would be interesting to see the effects of small amounts of carbohydrate food in reducing the excretion of these bodies after a long fast. Insulin alone might cause a temporary diminution by suddenly calling upon the small carbohydrate stores of the body. This would be a dangerous experiment since it might cause "insulin shock" a point recently emphasized by Talbot⁵ who found the blood sugar very low in some of his fasting epileptic children. Adrenalin would probably

¹ Shaffer: *Jour. Biol. Chem.*, 1921, **49**, 143.

² Wilson, Levine and Rivkin: *Am. Jour. Dis. Child.*, 1926, **31**, 335.

³ Brugsch: See Bönniger and Mohr, *Ztschr. f. exp. Path. u. Therap.*, 1906, **3**, 675.

⁴ Grafe: *Ztschr. f. physiol. Chem.*, 1910, **65**, 27.

⁵ Talbot, Shaw and Moriarty: *Jour. Am. Med. Assn.*, 1924, **83**, 91; Shaw and Moriarty: *Am. Jour. Dis. Child.*, 1924, **28**, 553.

have a similar effect as the result of a sudden mobilization of glucose. This may be of practical importance when a starving man seems to need sudden stimulation.

Water Starvation.—In all the long starvation experiments which have been made on human beings, water has been allowed throughout the fast. Under ordinary atmospheric conditions it is probable that a starving man could live for a long period without drinking any water. We must remember that the oxidation of 100 grams of fat produces 107 grams of water and the oxidation of 100 grams of dry protein, 41 grams of water. Levanzin, on the twenty-first day of his fast, metabolized 47.6 grams of protein, 112 grams of fat. From these sources he derived 140 grams of water. Benedict¹ calculates that on this day he derived 190 grams from the breaking down of flesh and 11 grams from fatty tissue. Thus we see that a total of 341 grams of water was available on this day. On this same day, it is estimated that he vaporized from the skin and lungs 485 grams of water, but on the previous day he had lost only 236 grams. Under such conditions, in order to obtain the water necessary for the urinary secretion there would be a dehydration of the tissues of the body, but experience has shown that the body has large stores of water which can be drawn upon before serious results intervene. In starving patients the factors which would increase the water loss from the body are diarrhea, diuresis, fever, sweating, excessive protein breakdown with large urea formation and warm air. The most horrible examples of water deprivation have been found in men lost in the desert.² One such case has been graphically described by King.³

A number of experiments in water starvation have been made in animals. Rubner⁴ found that starving pigeons die in four to five days, while those allowed water and no food live twelve days. Pigeons fed dry food die in about four and a half days. Straub⁵ fed a dog nothing but dry meat powder mixed with fat. The muscles lost 20 per cent of their water content.

¹ Benedict: Carnegie Institution of Washington Publication No. 203, 1915, p. 409.

² Rowntree: *Physiol. Rev.*, 1922, **2**, 116.

³ King: *Am. Jour. Med. Sci.*, 1878, **75**, 404.

⁴ Rubner: von Leyden's *Handbuch der Ernährungstherapie*, 1903, **I**, 53.

⁵ Straub: *Ztschr. f. Biol.*, 1899, **38**, 537.

Chronic Inanition.—Comparatively few of our patients show the phenomena of complete starvation, but most of them are suffering from more or less chronic inanition. The discussion of this subject, therefore, constitutes one of the most important chapters of this book. A few years ago particular attention was given to the so-called deficiency diseases which result from a lack of vitamins. In Europe, war edema and xerophthalmia made their appearance. Scurvy is still occasionally seen, pellagra is common in the Southern states, beri-beri seems to have almost disappeared. As a matter of fact, all of these deficiency diseases are rarities in the adult wards of the hospitals in the northern parts of our country. Rickets is still common among the children of our cities and many adults still show its effects in the skeletal development but the process is no longer a factor in their metabolism. Unfortunately, time does not permit a discussion of the deficiency diseases.

The subject of chronic undernutrition has been adequately reviewed by Lusk,¹ Benedict and his collaborators,² and Morgulis.³ It was Magnus-Levy⁴ in 1906 who first called attention to the profound alteration in the basal metabolism caused by undernutrition. His patient was a barber, aged nineteen years, of neurasthenic disposition, who had lived for nine months on an exceedingly low diet in an effort to cure constipation. He entered the hospital a living skeleton with a temperature of 36.1° to 36.5° C. For five days he was kept on his previous diet which was found to contain 700 to 800 calories. At this time his basal metabolism was 33 per cent below the average normal. He was then given abundant food and the heat production rose in a few days until it was only 17 per cent below the average. Later, he developed a fever from tuberculosis. When he recovered from this his metabolism was normal. The results are shown in Table 48. It was later noted by Svenson⁵ and others that emaciated typhoid convalescents showed in some instances heat production considerably lower than normal men. These results were recalculated in terms of surface according to Meeh's

¹ Lusk: *Physiol. Rev.*, 1921, **1**, 523.

² Benedict: Carnegie Institution of Washington Publication No. 280, 1919.

³ Morgulis: *Fasting and Undernutrition*, New York, Dutton & Co., 1923.

⁴ Magnus-Levy: *Ztschr. f. klin. Med.*, 1906, **60**, 177.

⁵ Svenson: *Ztschr. f. klin. Med.*, 1901, **43**, 86.

TABLE 48.—METABOLISM EXPERIMENT ON MAGNUS-LEVY'S PATIENT.*

Period.	Date.	Condition.	Calories per sq. m. per hour, height-weight formula.	Weight, kg.	Relationship of metabolism to average normal 39.7, per cent.
I . .	Nov. 16 to 21	Very low diet	26.6	36.2	-33
II . .	Nov. 23 to Dec. 9	Liberal diet	33.0	38.0	-17
III . .	Jan. 26 to Mar. 6	Fever from tb.	43.4	48.4	+9
IV . .	Mar. 13 to May 8	Normal again	40.5	52.2	+2

* Age, nineteen years; height, 160 cm.

formula by Coleman and Du Bois.¹ Allen and Du Bois² noted a similar reduction in emaciated diabetics. They calculated that some of their patients and those reported by Benedict and Joslin³ give results 15 to 19 per cent below the average. They also pointed out the unusually low metabolism of many of the normal controls used by Benedict and Joslin. These were naturally thin men who had been selected because they most nearly resembled the patients in height and weight. Interesting proof came from Germany in 1916 and 1918. Zuntz and Loewy⁴ have been making important contributions to the science of the respiratory metabolism for many years and have, during this period, made many determinations of their own basal metabolism. The results on Zuntz are shown in Table 49. His metabolism

TABLE 49.—METABOLISM OF ZUNTZ. (TAKEN FROM LUSK.⁵)

Year.	Age.	Weight, kg.	O ₂ cc. per minute.	Calories per square meter (Meeh) per day.
1888	41	65.2	236	804
1901	54	67.6	231	780
1903	56	67.6	228	773
1910	63	68.5	235	792
1916	69	60.6	198	709
1917	70	59.4	198	723

¹ Coleman and Du Bois: Arch. Int. Med., 1914, 14, 168.

² Allen and Du Bois: Clin. Cal. 17, Arch. Int. Med., 1916, 17, 1010.

³ Benedict and Joslin: Carnegie Institution of Washington Publication No. 136, 1910; Publication No. 176, 1912; Deutsch. Arch. f. klin. Med., 1913, 111, 333.

⁴ Loewy and Zuntz: Berl. klin. Wchnschr., 1916, 53, 825; Zuntz and Loewy: Biochem. Ztschr., 1918, 90, 244.

⁵ Lusk: Phys. Rev., 1921, 1, 523.

had shown no reduction up to the age of sixty-three. The war reduced his body weight 8 or 9 kilograms and his heat production dropped about 15 per cent. Loewy's fell about 12 per cent at a time when his body weight had decreased 22 per cent. Loewy's metabolism later rose at a time when the nitrogen excretion had risen to 17 grams on an intake of 7 to 8 grams.

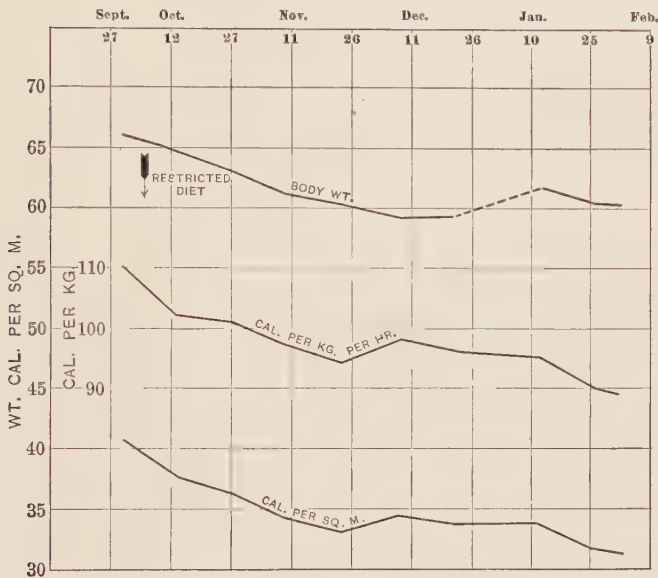


FIG. 43.—F. G. Benedict's experiment on undernourished students. In Squad A the diet was restricted in October. There was a steady fall in body weight, calories per kilogram and calories per square meter.

Benedict's Y. M. C. A. Students.—Under the stimulus of the war with its necessity for food reduction, Benedict and his associates, Miles, Roth and Smith,¹ made an elaborate study of a number of students who were placed on a diet low in calories but adequate in protein and vitamins. A group of twelve athletic young men (Squad A) before the test were taking 3200 to 3600 net calories a day. They were then placed on a diet of 1400 calories for three weeks, without reducing their mental or physical activities. After the average weight had fallen 12 per cent below its original level, it was

¹ Benedict, Miles, Roth, Smith: Carnegie Institution of Washington Publication No. 280, 1919.

found that they were able to maintain this weight on a diet of 1950 calories, a little more than one-half of the amount originally required. Meanwhile, the heat production during sleep had fallen to about three-quarters of its original figure and the heat production, per kilogram of body weight and per square meter of body surface, was about 18 per cent lower than at the beginning of the study. There was, of course, a pronounced loss of body nitrogen, the average for each man during the whole experimental period being 150

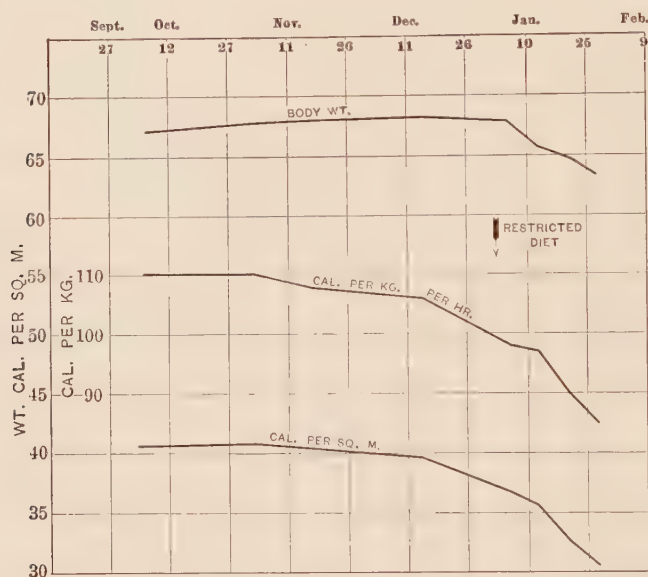


FIG. 44.—F. G. Benedict's control group of students. The restricted diet was begun in January. Note the sharp fall in metabolism and weight.

grams. The pulse-rate was greatly lowered, some morning rates being as low as 33 per minute. Systolic and diastolic pressures were distinctly lower. The rectal temperature remained normal. There was a slight falling off in the strength tests but the muscular efficiency did not seem to be impaired. In fact, actual measurements proved that on account of their lower weights they were able to walk a mile with less expenditure of energy than at the beginning of the experiment. Numerous tests of the neuromuscular processes showed no striking change. On the other hand, the men do not seem to have been particularly happy or comfortable. They were

hungry and as expressed in their college slang, "lacked pep." In other words, they did not feel as active and energetic as before. They felt the cold more keenly than their fellows. No harm resulted from the experiment in any case.

TABLE 50.—THE RESULTS UPON THE ELEVEN YOUNG MEN COMPOSING SQUAD A.

	During normal diet (3000 calories) September 29-30.	End of period with re- duced diet January 26-27.	Per cent reduction.
Basal metabolism in calories . . .	1686.0	1367.0	19.0
Calories per kilogram . . .	25.2	22.3	11.5
Calories per square meter body surface	940.0	788.0	16.2
Body weight in kilograms* . . .	67.0	61.3	8.5

* Calculated from above data.

TABLE 51.—SQUAD B.

	During normal diet.	End of period of 1375 calories.	Per cent reduction.
Basal metabolism in calories . . .	1745.0	1293.0	32.0
Calories per kilogram . . .	25.7	20.4	20.0
Calories per square meter body surface	872.0	647.0	27.0
Body weight in kilograms . . .	67.9	63.4	6.5
Body nitrogen in grams	2037.0	1972.0	3.2

Lusk¹ has reviewed this important experiment and has recalculated some of the results, paying particular attention to the relationship between loss of body nitrogen and reduction in metabolism. He points out that in the twelve men of Squad B who were used first as controls for Squad A and later placed on a diet of 1375 net calories containing 8.19 grams of nitrogen for three weeks, the average daily loss of nitrogen was 3.1 grams, the average total loss, 65 grams. Lusk calculates that this was a loss of only 3.2 per cent of the total nitrogen originally in the body. The average body loss was 6.5 per cent of the original body weight or 4.4 kilograms, approximately half of the material lost being protein-containing tissues. Lusk summarizes the results in Tables 50 and 51. It is evident that there is a striking discrepancy between the marked reduction in basal metabolism and the loss in body weight in kilograms and the loss of body nitrogen. He points out that there is not only a mechanism of nitrogen

¹ Lusk: *Physiol. Rev.*, 1921, 1, 523.

minimum protecting life from destruction but also a biological adaptation to a lowered energy intake, preventing the exhaustion of the reserve of body fat.

The men of Benedict's squads were apparently able to perform a considerable amount of work without discomfort and without any loss of muscular efficiency. Joffe, Poulton and Ryffel¹ also found no alteration in the muscular efficiency of a greatly undernourished individual. Benedict's men were not pushed to the point of exhaustion and we do not know whether or not this would have occurred sooner than in normal men. Their general physical reaction has been described by Benedict as follows:

1. Feelings of general weakness and tiredness, a condition commonly expressed in college slang as lack of "pep" or drive, when it seemed to require more energy to accomplish a given amount of work and it was necessary to urge one's self harder.

2. Weakness of the legs and accompanying unpleasant sensations of fatigue, particularly in stair-climbing.

3. Subnormal gymnasium and athletic performance, as shown by inability to continue the rapid calisthenics or to do the heavy apparatus work for the prescribed time and with the usual subjective satisfaction and generally to produce effectively sudden bursts of energy. There was also a marked diminution in sex expression coincident with the reduced diet. This was noticed in Germany during the World War and it has frequently been observed in animals.

In Germany, experiments were made by Jansen² on some students who attempted heavy work while on the official Munich rations, containing 60 grams of protein and 1628 calories. Walks of 11 to 16 miles in a driving snowstorm exhausted the men. On the whole this seems to have been an unusually severe test. Anderson and Lusk³ had shown in 1917 that the muscular efficiency of a dog was not greatly changed by thirteen days of fasting. They determined the basal metabolism of the dog before the fast and found that it required 0.550 kilogram-meters of energy to move 1 kilo of body weight 1 meter when the animal was running on a treadmill inside a calorimeter at a rate of 3 miles an hour.

¹ Joffe, Poulton and Ryffel: *Quart. Jour. Med.*, 1919, **12**, 334.

² Jansen: *Deutsch. Arch. f. klin. Med.*, 1917, **124**, 1.

³ Anderson and Lusk: *Jour. Biol. Chem.*, 1917, **32**, 421.

After thirteen days of fasting, the animal had lost 20 per cent of its weight and required 0.584 kilogram-meters to move 1 kilogram 1 meter. The total work done was, of course, reduced on account of the lower weight of the animal. The basal metabolism was reduced 28 per cent at the end of the fast but after two weeks of the standard diet, it rose again to its former level. It is interesting to note that on the eighth and thirteenth days of fasting an amount of food with a caloric value equal to the hourly energy consumption was given. The mornings following this no rise in the basal metabolism was observed. Eighteen hours after the first day of standard diet there was still no rise. The authors conclude that the condition of the body and not a large influx of food on the day previous, determines the height of metabolism. It is interesting to note that Takahira¹ obtained a distinct fall in metabolism in most of his human subjects during the first few days of re-alimentation after long fasts. After the first few days there was a rapid rise in heat production, a rise in nitrogen metabolism with a great deposit of body protein and a respiratory quotient which remained higher than 1 twelve to fourteen hours after the last food thus indicating the continual transformation of carbohydrate into fat. The results obtained on Takahira himself are shown in Fig. 45. These same phenomena of the recovery process were emphasized by Coleman and Du Bois² when they discussed the convalescence from typhoid fever.

In this connection, we may refer briefly to the effects of diminishing the protein intake to an exceedingly low level in an animal receiving adequate supplies of carbohydrate and fat. The protein metabolism falls to the "wear and tear quota" or nitrogen minimum with an excretion of only 2 to 3 grams a day. Rabe and Plaut³ have actually noted the extraordinarily low output of 1 to 2 grams of nitrogen a day in a vegetarian accustomed to low-protein diet. The nitrogen losses of the body are much smaller than during complete starvation and it is probable that the reduction in metabolism is comparatively slight. Carbohydrate withdrawal is exemplified beautifully in diabetes and will be dis-

¹ Takahira: Report of the Metabolic Laboratory, The Imperial Government Institute for Nutrition, Tokyo, 1925, 1, No. 1.

² Coleman and Du Bois: Arch. Int. Med., 1914, 14, 168.

³ Rabe and Plaut: Deutsch. Arch. f. klin. Med., 1921, 137, 187.

cussed under that heading. A complete withdrawal of fats from the diet could not be tolerated by man for a sufficient period to make a noticeable change in the metabolism. Experiments on animals with diets containing no fat would be complicated by the lack of vitamins. The effect of with-

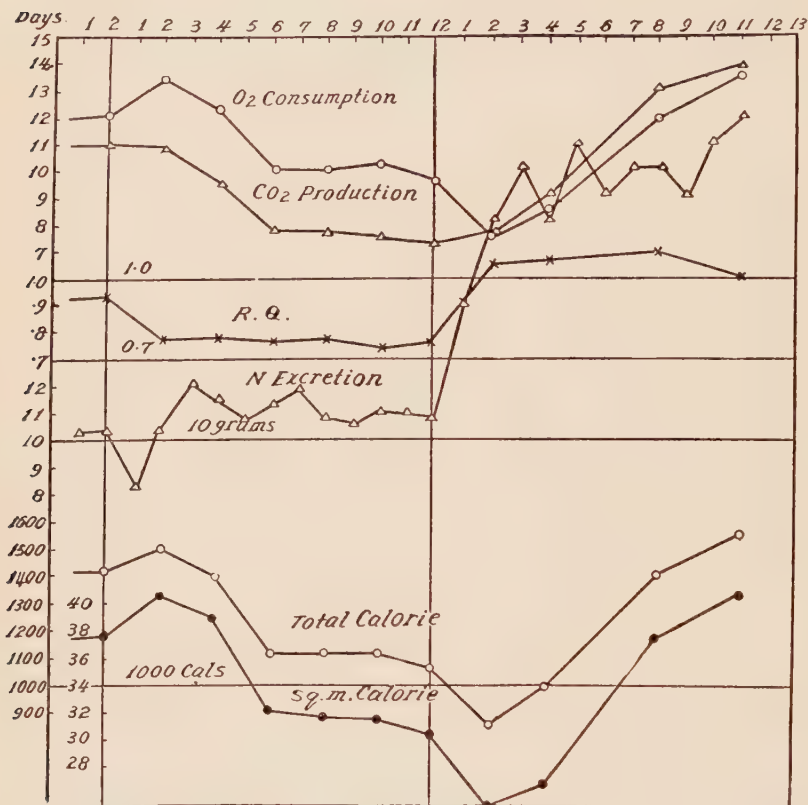


FIG. 45.—Results obtained by Takahira during his own fast of twelve days and during the period of re-alimentation.

drawing the various mineral constituents from the diet of man has not yet been sufficiently studied.

Moderate undernutrition such as is found in many people leading apparently normal lives does not seem to cause much change in the metabolism. Thus Blunt and Bauer¹ in a study of 16 underweight college women obtained an average

¹ Blunt and Bauer: Jour. Home Economics, 1922, 14, 171.

basal metabolism only 1.3 below the Harris-Benedict and 1.9 per cent below the Sage standards. They recalculated the data of Harris and Benedict on the 23 young women of their large series who were distinctly underweight. Their

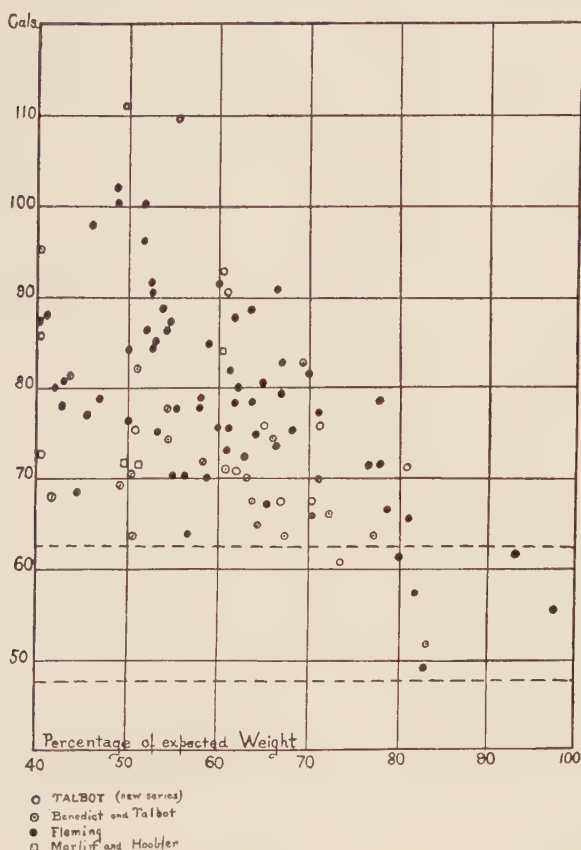


FIG. 46.—Chart showing the relationship between the calories per kilogram of undernourished children and the degree of weight deficiency. (Talbot.)

metabolism was only 1.8 per cent below the average of all the women examined by Harris and Benedict and only 3.2 per cent below the Sage standards.

In children the results are more striking and there is a tendency for the metabolism to be high instead of low. Talbot¹ has shown that undernourished infants have a metab-

¹ Talbot: *Am. Jour. Dis. Child.*, 1921, 22, 358.

olism much above the average for normal children both according to weight and surface area. There is of course a tendency for the total calories per day to be lower than in the case of a normal child of the same age since the atrophic infants are very small. Talbot ascribes the increase of metabolism per unit of body mass to a loss of inactive fat and a relative increase in active protoplasm. Murlin¹ believes the atrophic infant has a high metabolism because it loses heat more rapidly since the skin has no fat underneath it to act as a conserver of body heat. Boothby and Sandiford² emphasize the fact

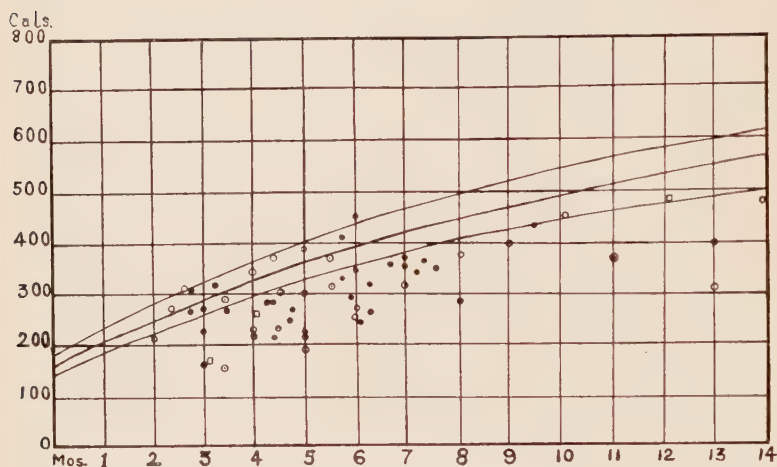


FIG. 47.—Chart showing that the total calories given off by an atrophic child is less than the normal for his age. The heavy curved line represents the average normal. (Talbot.)

that the children are sick and not to be compared with healthy adults on low diets. They ascribe the increased metabolism to the same factor which causes the illness. Probably all of these elements are important.

This tendency toward increased metabolism with undernutrition seems to extend to the ages of eight to twelve years according to the studies of Blunt, Nelson and Oleson.³ They examined 28 underweight school children and found the basal metabolism averaged 15 to 25 per cent higher than the

¹ Murlin: *Abt's Pediatrics*, Saunders and Co., Phila., 1923, 1, 520.

² Boothby and Sandiford: *Phys. Rev.*, 1924, 4, 69.

³ Blunt, Nelson and Oleson: *Jour. Biol. Chem.*, 1921, 49, 247.

various Benedict and Talbot standards. Recalculated according to the Sage curve their metabolism is slightly low. The standards at this age are not satisfactory but the Benedict-Talbot figures are probably more suitable for purposes of comparison with this series of underweight children.

Wang, Kern, Frank and Dunwiddie¹ noted a moderate increase in undernourished children four to thirteen years old. They believe that the subjects were probably deficient in their fat stores and that their actual tissue metabolism still approximated that of normal children.

¹ Wang, Kern, Frank, and Dunwiddie: Jour. Biol. Chem., 1925, **63**; Scientific Proceedings, XIX, p. lxi.

CHAPTER XI.

OVERNUTRITION AND OBESITY.

THE condition of overnutrition is prevalent in our country and obesity is one of the most common diseases. Perhaps it is more discussed by the laity and the public press than any other nutritional disorder. The large amount of public interest is in marked contrast to the small amount of scientific information. We do not yet know why certain individuals grow fat. Perhaps it would be more accurate to say that we do not know why all the individuals in this overnourished community do not grow fat. There is no stranger phenomenon than the maintenance of a constant body weight under marked variation in bodily activity and food consumption. To take a specific instance, a man, aged forty years, now weighing 165 pounds (75 kilograms) weighed the same amount twenty years ago. If during that period he has consumed an average of 2500 calories a day, the total for the twenty years would amount to 18,250,000 calories. The amount of extra fat stored in or lost from the body could hardly be more than 1 kilogram or 9300 calories. This means that the total intake of food must have been adapted to the total expenditure with an error of only 0.05 of 1 per cent. This is an extraordinary exactness which is equalled by few mechanical devices and almost no other biological processes. Does it mean that the individual appetite has unconsciously balanced the bodily needs with such extreme delicacy? There are many people who maintain constant weights during these decades without any conscious limitation or increase in their dietaries. There are many in this civilized land who maintain a constant weight only by frequent use of weighing machines and careful observations of the tightness of the waist bands of skirts or trousers. We must remember, however, that obesity is rarest in those savage tribes where bathroom scales are unknown and skirts and trousers at a minimum.

In the large class of people who are obliged to control their weight, slight reductions in the diet or increases in the daily

exercise are usually sufficient. In some individuals, however with apparently good endocrine glands, the weight increases to the point where it exceeds the normal limits. These are the cases of so-called simple or exogenous obesity. The term exogenous indicates that there is no endocrine disturbance, but that the fault lies either in too much food or too much laziness. It is not strictly exogenous because greediness and laziness certainly rest within the body. Neither is it simple because we often find that the cure is difficult.

Some of these obese patients obviously eat more than their neighbors, others obviously lead more sedentary lives. A few seem to be fairly active in their habits and frugal in their diets. These furnish us with the true problem of obesity. There are, in addition, many people who become fat after the age of forty as the result of some endocrine disturbance but these will be discussed later.

Regulation by Appetite.—In the normal man, we may assume that the adjustment of expenditure and intake is made in the following manner: His food for a given day is determined by his appetite which corresponds roughly to the demands made by the muscular activity of the previous twenty-four hours. Some of the food is deposited in the depleted store-houses of the body. Some of it which is not so deposited produces a rise in metabolism on account of its specific dynamic action. This, on the average, only amounts to 6 per cent of the caloric value of the food, but after a heavy meal, especially one containing protein, it may rise to 30 or 40 per cent. In this manner, some of the excess food is burned and wasted just as a surtax diminishes a large income. There may still be an excess of intake over expenditures. This is usually stored as body fat and we must remember that it only requires 3 ounces (100 grams) of fat to contain an excess of 900 calories. When well nourished, the individual tends to become more energetic and it is quite possible that he will soon burn up his stored fat by extra work or exercise which would not have been undertaken had it not been for the over-feeding. Even if the store of a few ounces of fat remains for a few days or a few weeks it may be called upon at a time when there is a temporary depression of the appetite below the point where it balances the requirement.

Let us suppose that at another time this same individual eats less than enough on a given day to cover that day's

need. The food, after it has been digested, is transported to the depleted tissues with little or no specific dynamic action and is thus utilized more economically. The deficit in calories is made up by drawing upon the body protein, glycogen and fat. Should this deficit continue for many days there would be, as we have seen, in the last chapter, a gradual lowering of the basal metabolism and a tendency toward restriction of activities due to a lack of energy and initiative. There would also be in a normal man an increased appetite which would repair all previous losses as soon as sufficient food became available. Incidentally, we may ask ourselves why a given individual 5 feet 10 inches tall with a normal weight of 165 pounds shows an increased appetite if his weight drops to 160 pounds, whereas, there are thousands of his contemporaries of equal height who habitually carry a weight of 160 pounds without any increased appetite. It is possible that a diminution of an individual's fat stores below the point habitual for that individual causes an increase in appetite. A stationary body weight may, however, be deceptive. The well-known fact that some fat people do not lose weight on long periods of diet restricted below their estimated expenditure has recently been investigated by Strouse¹ and his associates who review the literature and add some cases of their own. The matter will be discussed more fully under the heading of "Body Weight." We cannot attack the law of the conservation of energy and we must assume that body fat is oxidized and replaced by water.

From this discussion, we can see that it is possible for the body weight to be maintained at a constant level by a fairly delicate adjustment of processes with which we are already familiar. It is not necessary to assume an interference of the ductless glands in normal men. In pathological cases, however, the effects of these glands are striking.

Basal Metabolism and Surface Area.—The earlier literature of the metabolism in obesity has been reviewed by von Noorden² and more recently by Tileston,³ Strouse and Lauter.⁴

¹ Strouse and Dye: *Arch. Int. Med.*, 1924, **34**, 267; Strouse, Wang and Dye: *Ibid.*, 1924, **34**, 275.

² Von Noorden: *Metabolism and Practical Medicine*, Chicago, W. T. Keener & Co., 1907, vol. 1; *Die Fettsucht*, 2d edition, Vienna and Leipzig, 1910.

³ Tileston: *Endocrinology and Metabolism*, New York and London, Appleton & Co., 1922, **4**, 29.

⁴ Lauter: *Deutsch. Arch. f. klin. Med.*, 1926, **150**, 315.

Much of the older work is difficult of interpretation on account of inadequate methods of comparing very stout patients with normal controls. If we are trying to determine whether or not the heat production of a stout individual is above or below normal level, there is obviously an error if we take the total oxygen consumption and compare it with that of smaller men. The error is only a little less marked if we compare the results according to kilograms of body weight, because a large proportion of the kilograms of the fat individual are nothing but inert fat which probably has little or no active metabolism. The surface area seems to give us the best means of comparison. Up to 1915, the method for determining surface area used by the German investigators who did practically all the work on obesity was that of Meeh.¹ According to this formula the surface is proportional to the two-thirds power of the weight and the factor of height is entirely neglected. It is obvious that a thin man, 6 feet 2 inches tall, weighing 165 pounds, would have a much larger surface area than a stout man of the same weight who is only 5 feet tall. An error of +36 per cent in Meeh's formula in the surface area of a very fat woman was demonstrated by Du Bois and Du Bois.² The average error for normal individuals was about 12 per cent. The so-called linear formula of these authors determined the surface area by measuring the various parts of the body and gave an error of only +2 per cent in the one obese woman in whose case the method was tried. Their later "height-weight" formula used only these two factors and a constant and gave fairly close results on this same woman. In all the more recent work on obesity, either the linear formula or the height-weight formula has been applied to the individuals studied. It is the most accurate method available at the present time, but, unfortunately, has been tested on only one very fat person. Benedict³ has found in one very stout man that the linear formula checks closely with his photographic method of determining surface area. Means⁴ in 1915, using the newer surface area methods, demonstrated that the metabolism of two women with simple obesity was within the normal limits. He gives a table sum-

¹ Meeh: *Ztschr. f. Biol.*, 1879, **15**, 425.

² Du Bois and Du Bois: *Clin. Cal. 5, Arch. Int. Med.*, 1915, **15**, 868.

³ Benedict: *Am. Jour. Physiol.*, 1916, **41**, 275.

⁴ Means: *Jour. Med. Res.*, 1915, vol. **32** (new series, **27**, 121).

marizing the earlier work done on this subject.¹ Boothby and Sandiford² have given a summary of their findings in 8614 cases of various conditions compared to the Sage normal standards using the height-weight surface-area formula. They tabulated 94 cases of obesity. Eighty-one per cent of these are within 10 per cent of the average normal; 95 per cent of them show basal metabolic rates between -15 per

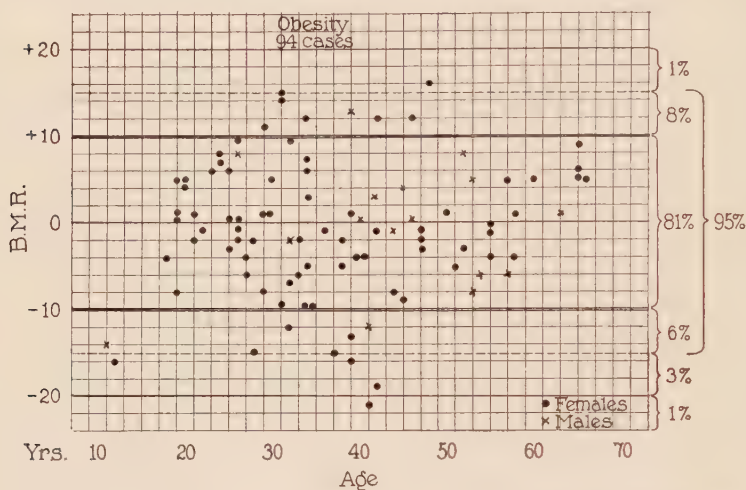


FIG. 48.—Ninety-four obesity patients studied by Boothby and Sandiford.

cent and $+15$ per cent; 3 per cent of the cases are between -20 and -16 . One individual is below -20 and 1 above $+16$. Calculated according to the Harris-Benedict prediction tables, the results are essentially the same. More recently several German investigators using these Benedict standards have obtained figures surprisingly close to the normal. Strouse, Wang and Dye³ have compared the basal metabolism of normal men and women and a large number of persons underweight or grossly overweight. They have found practically no difference in the calories per square meter

¹ Willebrand: *Skand. Arch. f. Physiol.*, 1901, 20, 152. Magnus-Levy: *Ztschr. f. klin. Med.*, 1897, 33, 302. Thiele and Nehring: *Ztschr. f. klin. Med.*, 1896, 30, 41. Stüve: *Arbeit. aus dem. Städt. Krankenhäuse zu Frankfurt, a. M. Festschrift*, 1896, 1, 44. Von Noorden: *Die Fettsucht*, Hölder, Leipzig and Vienna, 1910. Jacquet and Svenson: *Ztschr. f. klin. Med.*, 1900, 41, 375.

² Boothby and Sandiford: *Jour. Biol. Chem.*, 1922, 54, 783.

³ Strouse, Wang and Dye: *Arch. Int. Med.*, 1924, 34, 275.

of surface. This furnishes conclusive proof of the normality of the basal metabolism in simple obesity.

Specific Dynamic Action in Obesity.—The mere determination of the basal metabolism of subjects who are already obese is in many cases purely static in its nature and gives us only the end results after the condition has been fully established. Determinations fourteen hours after the last food are presumably made at a time when there is little active deposit of fat. It is for this reason, that tests made shortly after ingestion of food are important when compared with similar tests on similar normal individuals. Unfortunately, similar normal individuals do not exist and allowance must be made for the fact that the obese always have the higher total energy consumption on account of their greater weight.

Jaquet and Svenson¹ seem to have been the first to observe a diminished specific dynamic action in obesity. Rolly,² Plaut³ and Liebesny⁴ have all confirmed this diminution in the rise in metabolism after taking food. The subject has been studied in some detail by Wang, Strouse and Saunders⁵ who found the greatest depression of the curve in obese subjects after protein with relatively slight changes after carbohydrate and fat. Their results are shown in Figs. 49 and 50. We must remember that the average specific dynamic action throughout the day only amounts to 6 per cent of the total metabolism. If this were halved in obesity it would make the metabolism only 3 per cent below normal, a figure which would not explain the enormous discrepancies between the food intake and weight change observed by Strouse and others. Muscular activity is a much greater factor than the specific dynamic action in determining the total expenditure of energy. Pollitzer and Stolz⁶ have criticized the test-meal used by Liebesny and have studied the curves after giving protein and carbohydrate alone.

The most important recent work on obesity is that of Lauter⁷ in Friedrich von Müller's Clinic. He studied a large number of patients of both the endogenous and exogenous

¹ Jaquet and Svenson: *Ztschr. f. klin. Med.*, 1900, **41**, 375.

² Plaut: *Deutsch. Arch. f. klin. Med.*, 1922, **139**, 285. *Ibid.*, 1923, **142**, 266.

³ Rolly: *Deutsch. Med. Wchnschr.*, 1921, **47**, 877, 917.

⁴ Liebesny: *Biochem. Ztschr.*, 1924, **144**, 308.

⁵ Wang, Strouse and Saunders: *Arch. Int. Med.*, 1924, **34**, 573.

⁶ Pollitzer and Stolz: *Wien. Arch. f. inn. Med.*, 1924, **9**, 307.

⁷ Lauter: *Deutsch. Arch. f. klin. Med.*, 1926, **150**, 315.

types and came to the conclusion that there was no essential difference in their metabolism. Only a few in each group showed a basal heat production below the Harris-Benedict

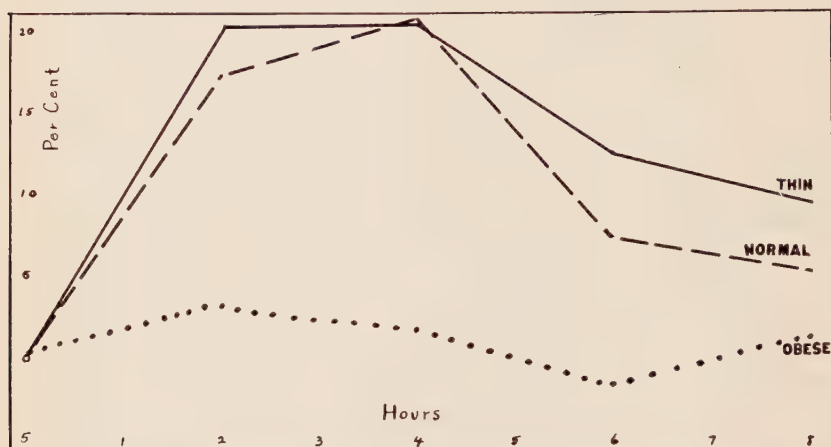


FIG. 49.—Average percentage increase of energy production after the ingestion of a meal containing 40 to 68 grams of protein. (Wang, Strouse and Saunders.)

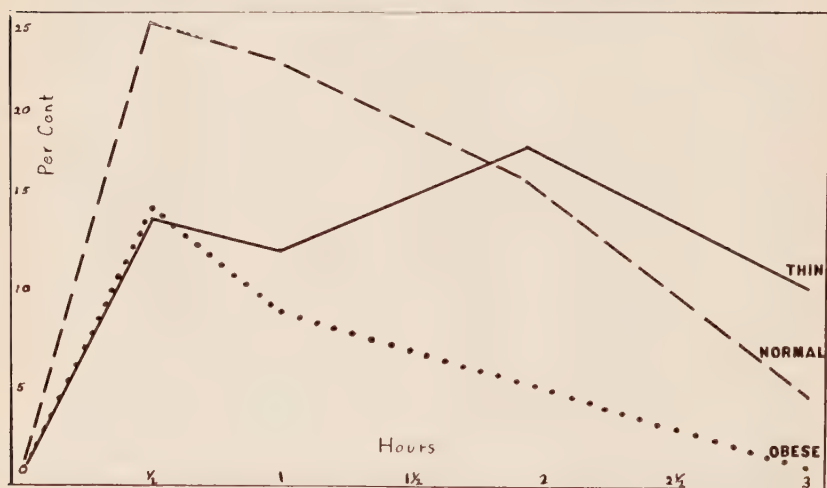


FIG. 50.—Average percentage increase of energy production after the ingestion of 80 to 106 grams of sucrose. (Wang, Strouse and Saunders.)

standards. Their total metabolism was, of course, much larger than that of a normal person of the same height, and often much greater than the normal man's basal metabolism plus his specific dynamic action. Lauter was unable to find

a significant difference between the normal controls and the obese patients studied for six to eight hours after a meal of 200 grams of beef. He criticizes the work of those clinicians who stop their tests two hours after the meal. In his investigation of the oxygen consumption after exercise, he noted that fat men recovered more slowly and that their muscular efficiency was apparently diminished.

Convincing studies on the muscular efficiency of fat people seem to be lacking. It is probable that most bodily activities would be accomplished with an abnormally high expenditure of calories on account of the extra body weight. It is, of course, possible that sleep in the obese is accompanied by an abnormal lowering of metabolism, but there is as yet no evidence one way or the other.

We must conclude that simple or constitutional obesity, which seems to be in many cases an hereditary disease, is accompanied by no abnormality of metabolism striking enough to be demonstrated by our present methods. Von Noorden pointed out many years ago that a daily excess consumption of 200 calories would lead in the course of a year to a deposition of 7.8 kilograms of fat. Let us return to the normal man who weighed 75 kilograms at the age of twenty years. If, instead of maintaining the same weight for 20 years, he had doubled his weight, the body would have added 75 kilograms of fatty tissue which would have contained 65 kilograms of fat according to the analysis of Bozenraad.¹ This represents an average daily gain to the body of 8.9 grams of fat, the amount contained in 11 grams of butter. It is appalling to think of the serious results that follow the unnecessary consumption of 1 butter ball a day. The extra 11 grams of butter will furnish enough energy to walk about $1\frac{1}{3}$ miles at a slow rate, so we can calculate that the obese man has either taken 11 grams of butter too much or else has walked $1\frac{1}{3}$ miles too little each day.

In another place we will discuss the depression of metabolism found in hypophyseal obesity and thyrogenous obesity. Adiposis dolorosa or Dercum's disease has not yet been sufficiently studied. Neither has the obesity associated with the pineal gland. The conflicting results in obesity of genital origin are discussed in other places.

Overnutrition and "Luxus Konsumption."—For a long time it has been a firm belief in the minds of many physicians

¹ Bozenraad: *Deutsch. Arch. f. klin. Med.*, 1911, 103, 120.

that the condition of overnourishment is accompanied by a "Luxus Konsumption" or luxury consumption of energy. According to this view, an excess in nourishment would be burned up and not stored in the body. This would explain very nicely the maintenance of a constant body weight. It would furnish a plausible antithesis to the economy of metabolism which accompanies undernutrition. Although it resembles the specific dynamic action of food, it is not exactly the same because it is supposed to be present fourteen hours or more after the last meal, a period when the specific dynamic action no longer exerts its effects unless the previous meal has been unusually heavy. The chief exponent of this theory has been Ehrich Grafe of Rostock. Working with Graham¹ he made some experiments on a dog and found that overnourishment caused an increase in metabolism of 40 per cent over a basal taken after twenty-one days of starvation. Just why they should have taken for their base-line the abnormally low metabolism of starvation is not clear. Their work in maintaining constant weight in an overfed dog is not convincing, since it was impossible to determine exactly the bodily activity and loss of body water. Working with Koch² he studied two individuals on a "Mastkur." The first man had been emaciated before an operation to relieve a stenosis of the pylorus. His basal metabolism, according to the height-weight formula rose from -10 per cent to +27 per cent and the total heat production increased 80 per cent though the weight rose only 50 per cent. The specific dynamic action was also increased. An asthmatic boy with a voracious appetite gave similar results. Eckstein and Grafe³ found a rise of 8 to 37 per cent in the metabolism of an overnourished dog. In a bitch the castration with a diet three times greater than the caloric requirement caused a rise of 19 per cent in the metabolism. Another bitch, after thyroidectomy, showed no such "Luxus Konsumption." Armsby, Fries and Bramen⁴ noticed an increase of 36 per cent in the katabolism of cattle in the fattened state.

Grafe⁵ has reviewed this subject in his excellent monograph giving the results on 3 healthy men whose abnormally high

¹ Grafe and Graham: *Ztschr. f. physiol. Chem.*, 1911, 73, 1; Eckstein and Grafe: *Ibid.*, 1919, 107, 73.

² Grafe and Koch: *Deutsch. Arch. f. klin. Med.*, 1912, 106, 564.

³ Eckstein and Grafe: *Ztschr. f. physiol. Chem.*, 1919, 107, 73.

⁴ Armsby, Fries and Bramen: *Jour. Agric. Res.*, 1918, 13, 43.

⁵ Grafe: *Ergeb. der Physiol.*, 1923, 21, Part II, 1.

metabolism he ascribes to this phenomenon. The first was a thirty-two-year-old colleague who "astonishes his table companions with his enormous food consumption." His metabolism was 16.5 per cent above the average normal. The second was even higher, +39 per cent, but there were a few symptoms such as nervousness and vasomotor instability which suggested a possible thyrotoxic origin for the large appetite. The third, with metabolism 16 per cent above the normal also showed a disproportion between weight and food consumption. Grafe believes that the thyroid plays an important if not determining rôle in this luxury consumption. He points out that not all men exhibit this regulatory capacity, otherwise, there would be no obesity.

It is possible that the obesity due to hypophyseal disease gives us a hint as to the origin of the so-called constitutional obesity. The frank cases show marked stigmata of endocrine disturbance as well as obesity. It is conceivable that common obesity is the only manifestation of an endocrine disturbance, a disturbance so slight that it upsets the balance of intake and output by less than 0.1 of 1 per cent.

A side-light is thrown on obesity by its antithesis found in thin persons who cannot be fattened even by the earnest coöperation of physician and patient.

Helmreich and Wagner¹ have lent support to the "Luxus Konsumption" theory in their work on children. They studied 9 children first on a maintenance diet and then after a period of thirteen to thirty-two days during which they added 1200 to 1900 extra calories in the form of protein, or sugar, or fat. Following the weeks of overnutrition the basal metabolism was appreciably raised, 6 to 18 per cent after fat, approximately the same amount after sugar, and 14 to 25 per cent after protein. Helmreich believes that there is no absolute basal metabolism but that it is a function of the condition of nourishment. He believes that the cells establish their expenditure according to the stored reserves.

At the present time we can only say that the attractive theory of "Luxus Konsumption" has not been adequately demonstrated. There is some confirmatory evidence in the high metabolism of rapidly growing children and of convalescent patients who have suffered wasting diseases.

¹ Helmreich and Wagner: *Ztschr. f. Kinderh.*, 1924, 38, 206; Helmreich: *Biochem. Ztschr.*, 1924, 146, 153.

CONSTITUTIONAL OR ENDOGENOUS OBESITY.

Grafe's Discussion of Obesity.—The most striking discussion of the so-called constitutional or endogenous obesity is to be found in Grafe's comprehensive monograph.¹ He speaks without much enthusiasm of von Bergmann's² theory that the primary cause lies in the fat tissue itself, a sort of lipomotosis universalis. Such tissue would be hard to oxidize. Grafe believes that this is a plausible and stimulating hypothesis but there is no proof as to its correctness. Such a theory does not exclude an endocrine origin of constitutional obesity. In fact, Grafe is inclined to believe that there is some sort of endocrine disturbance as a factor in all of these cases, in contradistinction to the cases of exogenous obesity which arise from overnourishment or laziness. A frank glandular etiology is, of course, apparent in myxedema, obesity following castration and dystrophia adiposito-genitalis. Grafe is inclined to think that thyroid plays a great rôle, since he and Eckstein³ found that "Luxus Konsumption" depended on the presence of this gland. He believes that the well-known endogenous obesity which follows castration or the menopause and accompanies the condition known as eunochoidism is due to the lack of interstitial cells. The fact that obesity is sometimes absent in these conditions Grafe ascribes to a possibly compensatory hyperfunction of other glands more especially the thyroid. The obesity of Fröhlich's disease he ascribes to diminished secretion of the pars intermedia but is in doubt as to the causation of the dystrophia adiposogenitalis. He is inclined to believe that there is a functional disturbance of the hypophysis with no compensatory involvement of the thyroid.

Grafe points out that in obesity the weight does not always indicate the relationship of caloric intake and output. Great losses of body substance may be masked by an equally great retention of water. One of his patients with obesity following castration maintained for twenty-two days a constant weight on an intake of 8 to 11 calories per kilogram. He calculates that the body must have lost about 3300 grams of dry material which was balanced by an equal gain of water without the

¹ Grafe: *Ergeb. des Physiol.*, 1923, **21**, Part II, 197, 282.
II, 208.

² Von Bergmann: *Oppenheimer's Handbuch der Biochemie*, 1910, **4**, Part

³ Eckstein and Grafe: *Ztschr. f. physiol. Chem.*, 1919, **107**, 73.

TABLE 52.—ENDOGENOUS OBESITY WITH LOWERED METABOLISM.*

Patient.	Age in years and sex.	Weight, kg.	Height, cm.	Kind of obesity.	Total calories per 24 hours (normal).	Calories per kg.	Calories per sq. m. surface area formula.	Calories per hour and sq. m.	Author.
R. J.	18 F.	98.0	168	Constitutional	1731.0 (1822) [†]	17.7	806.9 (Du Bois)	33.6	Salomon. ¹
L.	25 F.	83.0	163	Ovarian (?), constitutional (hunger)	1460.0 (1034)	17.6	695.0 (Bouchard)	29.0	v. Bergmann. ²
?	30 M.	91.0	169	Hereditary, juvenile	1614.0 (1931)	17.7	781.2 (Du Bois)	32.6	Stähelin. ³
W. R.	13 M.	66.5	155	Dystrophia adiposo-genitalis	1434.0 (1818)	21.6	844.7 (Du Bois)	35.2	Hausleiter. ⁴
Kl.	13 F.	69.0	151	Thyrogenic	1220.0 (1795)	17.7	716.1 (Du Bois)	29.8	Hausleiter. ⁴
A. Sch.	15½ F.	39.7	128	Thyrogenic	998.4 (1203)	25.2	837.7 (Du Bois)	34.9	Grafe. ⁵
G. Tr.	17 M.	56.5	?	Dystrophia adiposo-genitalis (hypo-physical tumor)	1128.0 (1457)	20.3	745.2 (Du Bois)	31.1	Grafe. ⁶
W.	23 M.	86.0	167	Castration	1368.0 (1943)	15.9	682.3 (Du Bois)	28.3	Rolly. ⁷
E. H.	17 ?	175.0	170	Hereditary, juvenile	2612.0	14.9	904.8 (Du Bois)	37.7	Löffler. ⁷
Mrs. M.†	28 F.	87.0	161	Hypopituitary	...	17.2	746.4 (Du Bois)	31.1	Means. ⁸
N. K.†	15 M.	94.0	165	Hypopituitary	...	19.6	873.6	36.4	Means. ⁹

* Grafe: *Ergeb. d. Physiol.*, 1923, 21, 289.† Salomon: *v. Noorden's Samml. klin. Abhandl.*, Berlin, 1905, 66.‡ v. Bergmann: *Ztschr. f. exper. Path. u. Therap.*, 1909, 5, 646.§ Stähelin: *Ztschr. f. klin. Med.*, 1908, 65, 425.¶ Hausleiter: *Ztschr. f. exper. Path. u. Therap.*, 1915, 17, 413.

‡ Not on Grafe's chart.

§ Grafe: *Deutsch. Arch. klin. Med.*, 1920, 132, 41.¶ Rolly: *Deutsch. med. Wchnschr.*, 1921, 47, 887, 917.‡ Löffler: *Ztschr. f. klin. Med.*, 1919, 87, 280.§ Means: *Jour. Med. Res.*, 1915, 32, n.s. 27, 121.¶ Means: *Arch. Int. Med.*, 1916, 17, 704.

appearance of edema. The basal metabolism, in his opinion, lies within normal limits in the majority of cases of endogenous obesity provided one uses as a basis of comparison the modern surface area formulas. Some patients, and especially those studied during or soon after the period of growth, show a distinct diminution in metabolism and these he has grouped in Table 52. At the bottom of this table I have added two patients studied by Means. The patient of Rolly is of especial interest because his metabolism had been studied two and a quarter years previously before the removal of both testes caused the development of obesity with gain of 30 kilograms in weight. During this period the total metabolism scarcely changed and the 30 kilograms must have acted like so much inert ballast.

For an excellent discussion of the whole subject of obesity, the reader is referred to the previously mentioned work of Lauter.¹ He emphasizes that the biggest factor is muscular activity with all its internal components. The question is not "does the fat man eat much or little" but "does he eat too much in relationship to his activity." He goes on to say "a man whose quickness and activity are limited is thereby denied a means of increasing his metabolism which is much better fitted to diminish weight than a change in basal metabolism or in specific dynamic action. . . . The patient with endogenous obesity lacks not the possibility but rather the impulse to movement. The impulse to move, the activity and effectiveness are bound up closely with the endocrine system."

The treatment of obesity cannot be discussed at length in this book but mention must be made of the work of Mason² who employs a subcaloric diet with enough thyroid extract to maintain the basal metabolic rate at about +10 per cent. He says that the results are uniformly satisfactory but he warns against the employment of thyroid extract if it cannot be controlled by basal metabolism tests.

¹ Lauter: *Deutsch. Arch. f. klin. Med.*, 1926, **150**, 315.

² Mason: *Canad. Med. Assn. Jour.*, 1924, **14**, 1052.

CHAPTER XII.

BASAL METABOLISM IN DIABETES.

History of Treatment.—Diabetes is a disease which varies greatly from year to year, not on account of any changes in its own nature, but rather on account of the rapidly changing fashions in treatment. Following the work of Minkowsky and Naunyn and von Noorden, patients with diabetes were given liberal amounts of protein and fat and restricted amounts of carbohydrates. In skilful hands this diet worked well in all except the most severe cases. Allen instituted a new era beginning in 1914–1915. He demonstrated that glycosuria, acidosis, and many other symptoms could be made to disappear by starving the patient for a few days and then keeping him on a diet so low that a steady reduction of body weight followed. This treatment undoubtedly reduced the mortality in diabetes and it was almost universally adopted in America. Diabetics became very thin and in severe cases were reduced to skin and bones. A reaction began and some went so far as to say that it was better for a diabetic to be dead than to drag out his existence in perpetual hunger and weakness. The pendulum began to swing back to the old Naunyn dietary. Newburgh and Marsh treated a large number of diabetics with a high-fat diet and obtained results that compared well with those of starvation. This upset all theories for a time. Then Woodyatt and Shaffer worked out in masterly fashion the laws that govern acidosis showing that each fat molecule is completely oxidized only if a molecule of glucose is oxidized at the same time. This made it possible to construct a diet on a basis of a patient's carbohydrate tolerance, giving him all the calories possible without the appearance of acidosis. Of course many clinicians had been doing very much this sort of thing largely on an empirical basis. Just as the improved calculations were being adopted Banting discovered insulin which came into general use by 1923. Treatment was again revolutionized.

Basal Metabolism.—The importance of determining the total metabolism in diabetes was recognized at an early date,

for in no other condition is a well-adjusted diet so necessary. The history of the earlier researches in this field is well given by Benedict and Joslin¹ in their monograph on diabetes. The first important studies were those of Pettenkofer and Voit² in 1867. Livierato's³ work has not been generally accepted. Weintraub and Laves,⁴ Nehring and Schmoll,⁵ Robin and Binet,⁶ Magnus-Levy,⁷ and others studied diabetics for short periods on the Zuntz-Geppert apparatus. As usual Magnus-Levy had a clear insight and pointed out the difficulty of comparing the metabolism of a diabetic with that of a normal man. He showed that with emaciation surface area changes less than weight, and indicated the advantage of comparing metabolism according to height rather than weight.

In 1910 Du Bois and Veeder⁸ studied the metabolism of 1 patient with severe diabetes and 1 with glycosuria, probably of renal origin, in a respiration chamber of the Pettenkofer-Voit type. The observations lasted twenty hours and could not be considered basal because the subjects were allowed to eat, read and move about in bed. The results were compared with those of a normal control of approximately the same age, height and weight, who copied the activities of the patients while he was in the chamber. It so happened that repeated basal metabolism experiments on this same normal control showed that he was very close to the average normal. This type of experiment does not really determine the basal metabolism of diabetics, and for many years I neglected to pay much attention to this piece of work. Recently I have realized that a diabetic patient is under basal conditions for only a small portion of the day. For practical purposes the diet must be adjusted to the caloric demands of a patient who is moderately active, and we are greatly in need of such data in diabetes. All of the theoretical work on the FA/G ratio is full of guesses as to the actual calories expended by diabetics during the day. We need more of the long period experiments and it is unfortunate that they went out of

¹ Benedict and Joslin: Carnegie Institution of Washington Publication No. 136, 1910.

² Pettenkofer and Voit: *Ztschr. f. Biol.*, 1867, **3**, 380.

³ Livierato: *Arch. f. exper. Path. u. Pharmacol.*, 1889, **25**, 161.

⁴ Weintraub and Laves: *Ztschr. f. physiol. Chem.*, 1894, **19**, 603.

⁵ Nehring and Schmoll: *Ztschr. f. klin. Med.*, 1897, **31**, 59.

⁶ Robin and Binet: *Arch. génér. de médecine*, 1898, **10**, 283.

⁷ Magnus-Levy: *Ztschr. f. klin. Med.*, 1905, **56**, 83.

⁸ Du Bois E. F. and Veeder B. S.: *Arch. Int. Med.*, 1910, **5**, 37.

fashion with the advent of the smaller types of apparatus. Under conditions of "Zimmerruhe" the two diabetics of Du Bois and Veeder showed the same heat production as the normal man.

The first extensive work on the metabolism of diabetes was the 1910 monograph of Benedict and Joslin.¹ This and the subsequent publication in 1912² indicated an increase in metabolism in diabetes as it was seen and treated before the introduction of the starvation method. The interpretation of their data was questioned by Lusk³ who calculated that instead of a 15 to 20 per cent increase in severe diabetes the rise amounted to only 5 to 10 per cent. Magnus-Levy, in 1913, concluded that in mild diabetes the basal metabolism is normal but that in severe diabetes the oxygen consumption per kilogram is increased on the average about 20 per cent. High metabolism was later reported by Leimdörfer,⁴ Rolly,⁵ and Seib. In 1914, Allen and Du Bois began the study of the metabolism of diabetics undergoing the starvation treatment. Meanwhile the Russell Sage Institute of Pathology had been developing a new surface area method and a new set of standards, since it was evident that the older methods of comparison were not adequate. In the first place it is obviously incorrect to compare emaciated diabetics with well-nourished normals on the basis of calories per kilogram. In the second place the generally adopted Meeh formula for surface area was found to be grossly inaccurate. The Sage investigators used the average calories according to the new surface area method, recognizing the fact that undernourishment in itself caused a lowering of metabolism. Benedict and Joslin had employed for comparison normal men who resembled their diabetics in height and weight. Many of these showed a low metabolism, probably on account of undernourishment. It is still questionable as to which basis for comparison is the better. Allen and Du Bois⁶ in 1916 tabu-

¹ Benedict and Joslin: Carnegie Institution of Washington Publication No. 136, 1910.

² Benedict and Joslin: *Ibid.*, No. 176, 1912.

³ Lusk: *Science*, 1911, 33, 433; *Animal Cal.* 11, *Jour. Biol. Chem.*, 1915, 20, 555.

⁴ Leimdörfer: *Bio-Chem. Ztschr.*, 1912, 40, 326.

⁵ Rolly: *Deutsch. Arch. f. klin. Med.*, 1912, 105, 494.

⁶ Allen and Du Bois: *Clin. Cal.* 17, *Arch. Int. Med.*, 1916, 17, 1010.

lated their results with those of Magnus-Levy, Mohr,¹ and Benedict and Joslin, and concluded that the increase of the basal metabolism above the true normal level is generally absent or slight. They found during fasting a fall to 20 per cent below the normal and concluded that the level of the metabolism in diabetes is the resultant of a number of forces, for example, increased destruction of protein and perhaps other processes tending to increase metabolism, and undernutrition, muscular relaxation (as in prolonged confinement in bed), and other possible conditions tending to diminish metabolism.

Geyelin and Du Bois² made a preliminary report on the results obtained in Cyril K., a classical case of maximum severity showing marked improvement after a period of fasting. His metabolism in the early stages was distinctly elevated. This was probably due to his unusually high-protein metabolism, but the severe acidosis may have been a factor. The results in this and in two other unusual cases of severe diabetes were later discussed in detail in a paper by Gephart, Aub, Du Bois and Lusk.³ One of the patients was a woman reduced to skin and bones as a result of severe diabetes and prolonged undernourishment. Her metabolism was 37 per cent below the standard level and was about 60 per cent below the total number of calories she must have produced when she was at her normal weight. The Sage investigators were unable to establish any clear evidence that acidosis increases the metabolism. Bernstein and Falta⁴ reached similar conclusions, finding no increase in metabolism and no distinct effect of acidosis. After 1914, however, the factor of undernutrition tended to mask the influence of other factors. Wilder, Boothby and Beeler⁵ have made a detailed report on a classical case in the patient Bessie B. Her diabetes was of the severest type and the basal metabolic rate averaged -12 per cent with slight daily variations. These authors give a table of results in 31 patients with diabetes, finding a normal or low metabolism in all except 3 cases which were complicated by hyperthyroidism. They say:

¹ Mohr: *Ztschr. f. exper. Path. u. Therap.*, 1907, **4**, 910.

² Geyelin and Du Bois: *Jour. Am. Med. Assn.*, 1916, **66**, 1532.

³ Gephart, Aub, Du Bois and Lusk: *Clin. Cal. 24, Arch. Int. Med.*, 1917, **19**, 908.

⁴ Bernstein and Falta: *Deutsch. Arch. f. klin. Med.*, 1916, **121**, 95.

⁵ Wilder, Boothby and Beeler: *Jour. Biol. Chem.*, 1922, **51**, 311.

We also reviewed the available observations of others and can find in them but few deviations of the basal metabolic rates of patients with uncomplicated diabetes from the Du Bois normal standards, that may not be attributable to factors which would be equally effective in modifying the metabolic rates of non-diabetic persons.

Woodyatt¹ reports a series of severe but uncomplicated cases of diabetes, all with normal urinary nitrogens. The basal metabolic rates varies between +2 and -18 per cent.

Holten,² in Denmark, on the other hand, has found in severe diabetes an average increase of a good 10 per cent above the Harris and Benedict normal value.

By far the most complete and most important discussion of the metabolism in diabetes is contained in the monograph of Joslin.³ He analyzes the final results obtained in many years of work on 113 diabetics. A total of 661 metabolism experiments, with 2219 individual periods, are recorded. The first part of the work was done in calorimeters, then the Benedict Universal Respiration Apparatus was used, and finally the respiration chamber (cot chamber) which Joslin found extremely satisfactory. He used the Harris and Benedict prediction tables as a standard for normal. Before June, 1914, the diabetics were given diets rich in fat and protein and many showed acidosis. Their average basal metabolism was 12 per cent above the Harris and Benedict standard. After June, 1914, the Allen treatment was used and with undernutrition the average basal metabolism fell to -11 per cent. The women showed about the same changes as the men. Joslin points out that in a group of 20 diabetics with the extreme loss of 35 per cent of their body weight, metabolism fell on an average 22 per cent below the normal, giving a loss of 0.63 per cent in metabolism for 1 per cent of body weight. He contrasts this with the Y. M. C. A. students studied by Benedict,⁴ who lost only 10.5 per cent in weight, with an average fall in metabolism of 19 per cent, or 1.8 per cent fall in metabolism for each 1 per cent in weight. He believes this great difference was due to the fact that the nor-

¹ Woodyatt: *Endocrinology and Metabolism*, New York and London, D. Appleton & Co., 1922, 4, 263.

² Holten: *The Respiratory Metabolism in Diabetics and the Influence of Insulin upon it*. Doctor's thesis, Copenhagen, Levin and Munksgaard, 1925

³ Joslin, E. P.: *Carnegie Institution of Washington Publication No. 323*, 1923.

⁴ Benedict, Miles, Roth and Smith: *Ibid.*, No. 280, 1919.

mal men had a quicker loss and a quicker adaptability. In the whole series mild diabetics showed normal metabolism. With increasing severity, metabolism before 1914 tended higher; after 1914, lower. With increasing acidosis, there was a slight tendency toward increased metabolism, but the effect was not striking. The lowest metabolism was found in girls sixteen to eighteen years of age, one of whom gave a reading of -48 according to Harris and Benedict's standard and -50 according to the Sage standard. This is probably the lowest reading ever recorded. Menstruation and menopause had no distinct effect, and pregnancy caused a slight increase in metabolism.

Joslin made many experiments with levulose and found that its ingestion caused a greater rise of heat production than in the case of normal people. Even in rather severe diabetes it caused a rise in the respiratory quotient, but after the fifth half-hour this fell below the fasting level. Orange juice had a similar effect. Joslin makes an exceedingly interesting report on the metabolism of a normal woman who voluntarily underwent the fasting treatment, going four days without food and then following the usual régime of slow increases in the diet. Her basal metabolism showed very little change. Acidosis began on the third day of starvation and started to subside when the carbohydrate in the diet rose to 30 grams, which supplied enough calories to cover 15 per cent of the total metabolism.

After many years of interesting discussion we find now almost unanimous agreement with regard to the basal metabolism in diabetes. In mild cases there is no change from the normal. In severe cases, at the present time the patients are almost all undernourished and, on this account, show a lower metabolism than normal. This lowering is usually proportional to the degree of emaciation and in extreme cases may be 30 to 40 per cent below the average.

At the present writing it is impossible to say just what influence the insulin treatment will have on the basal metabolism in these severe cases. We should expect that their metabolism would return to normal as they gain weight and return to the condition of mild diabetes. Joslin¹ has given a table demonstrating that most cases show a gain in weight

¹ Joslin: *The Treatment of Diabetes Mellitus*, third edition, Philadelphia and New York, Lea & Febiger, 1923, p. 425.

and heat production on insulin treatment. Of the 11 cases reported only 3 showed no change. The others increased their metabolism 6 to 24 per cent.

The only patient with coma who has been studied in a respiration apparatus, as far as I can find, is the Finnish carpenter, Charles S., reported by Richardson and Mason.¹ His metabolism was 11 per cent above the normal standard during profound coma, at a time when his urine contained 24.3 grams of nitrogen per day and 33 grams of total acetone bodies. This was the only one of their patients who did not show a reduction in metabolism proportional to the reduction in body weight.

TABLE 53.—SPECIFIC DYNAMIC ACTION OF EXCESSIVE PROTEIN DESTRUCTION.
(CYRIL K.)

Date.	Urinary nitrogen in excess of normal basal per hour.	Extra calories due to specific dynamic action (extra $N \times 26.5 \times 0.764$).	Total calories per hour.	Total calories minus calories of specific dynamic action.	Calories (minus calories specific dynamic action) per sq. m. per hour.	Per cent below average normal.
Dec. 15, 1915	0.83	16.8	81.9	65.1	36.4	- 8
16, 1915	0.93	18.8	76.4	57.6	32.2	-19
18, 1915	0.42	8.5	73.2	64.7	36.1	- 9
20, 1915	66.3	37.0	- 7
22, 1915	62.8	35.9	-10

It is quite evident that a considerable number of patients with severe diabetes show an increased metabolism. The cause of this is not yet entirely explained. Most investigators at the present time believe that the increased protein metabolism is largely, if not entirely, responsible for the increase in total metabolism. Rubner² called attention to this many years ago. The Sage investigators³ emphasized this point in 1916 and again in 1917.⁴ They have calculated that the extraordinarily high-protein metabolism of the patient, Cyril K., caused such a large specific dynamic action as to account for 17 to 19 extra calories an hour. Bernstein

¹ Richardson and Mason: Clin. Cal. 33, Jour. Biol. Chem., 1923, 57, 587.

² Rubner: Die Gesetze des Energieverbrauchs bei der Ernährung, Franz Deuticke, Leipzig and Vienna, 1902, p. 310.

³ Allen and Du Bois: Clin. Cal. 17, Arch. Int. Med., 1916, 17, 1010.

⁴ Gephart, Aub, Du Bois and Lusk: Clin. Cal. 24, Arch. Int. Med., 1917, 19, 908-930, Table 8.

and Falta¹ consider the protein katabolism the chief factor in causing increase in total metabolism. Joslin² has recently reviewed the subject with great care and has brought out the point that in some of his patients a rise in nitrogen excretion, at one time associated with increasing metabolism and at another with decreasing metabolism, certainly suggests that the nitrogen metabolism in and of itself does not control the metabolism of the diabetic. He ascribes the increased metabolism rather to acidosis.

Total Metabolism and Acidosis.—In the two monographs by Benedict and Joslin³ attention is called to the relationship of acidosis and increased metabolism. Their interpretation was questioned by the Sage investigators.⁴ Wilder, Boothby and Beeler⁵ say that acidosis itself does not appear to elevate the basal metabolic rate; an increase in the rate, accompanied by an acidosis, is probably due to the factor that causes the acidosis. The subject is extremely complicated, and I doubt if it will ever be definitely settled. At the present time it seems as if a severe acidosis might cause a moderate increase in metabolism in some cases of diabetes.

Effect of Age on Basal Metabolism.—It is difficult to estimate the effect of age in modifying the total metabolism in diabetes. Joslin⁶ finds that in subjects between fifty-one and seventy years of age, the metabolism varied only 1 per cent from the Harris and Benedict standard. Between the ages of twenty-one and fifty years the average was 17 per cent above before June, 1914, and 10 per cent below the standard after the introduction of the Allen treatment. Between the ages of eleven and twenty years metabolism was 4 per cent above before 1914 and 4 per cent below afterward. In this decade the normal standards are not well established and it is quite possible that undernutrition and other factors have an unusually strong influence. Allen and Du Bois,⁷ in discussing

¹ Bernstein and Falta: *Deutsch. Arch. f. klin. Med.*, 1916, **121**, 95.

² Joslin: *Carnegie Institution of Washington Publication No. 323*, 1923, p. 120; *Treatment of Diabetes Mellitus*, third edition, Philadelphia and New York, Lea & Febiger, 1923, p. 240.

³ Benedict, F. G., and Joslin, E. P.: *Carnegie Institution of Washington Publication No. 136*, 1910; No. 176, 1912.

⁴ Allen and Du Bois: *Clin. Cal.* **17**, *Arch. Int. Med.*, 1916, **17**, 1010; Gephart, Aub, Du Bois and Lusk: *Clin. Cal.* **24**, *Arch. Int. Med.*, 1917, **19**, 908.

⁵ Wilder, Boothby and Beeler: *Jour. Biol. Chem.*, 1922, **51**, 311.

⁶ Joslin: *Treatment of Diabetes Mellitus*, third edition, Philadelphia and New York, Lea & Febiger, 1923, p. 211.

⁷ Allen and Du Bois: *Clin. Cal.* **17**, *Arch. Int. Med.*, 1916, **17**, 1010.

the low metabolism of children, reported by Benedict and Joslin, suggested that the normal stimulus of the growing organism may be checked by diabetes. The writer¹ has called attention to the fact that in typhoid fever the young subjects do not produce any more calories per unit of surface area than the adults.

Sex.—In diabetes, Joslin² finds that women have a lower metabolism than men, just as they do in health.

The Respiratory Quotient in Diabetes.—The level of the respiratory quotient depends chiefly on the proportion of carbohydrate metabolized. We therefore expect low quotients in diabetes and use the level of the quotient as an index of severity. There are certain conditions, however, in which the results require a special interpretation. It is not fair to say that a certain diabetic, who happens to show a low quotient, belongs in the severe group, unless we are certain that his quotient has been pushed as high as possible by a plentiful supply of available carbohydrate, since normal men show low quotients on low-carbohydrate diets. We should also consider the fact that the respiratory quotient merely indicates the percentage of calories furnished by carbohydrate and not the total number of calories unless we make a special calculation. This means that a very thin patient with low metabolism may have a rather high quotient, although he can metabolize very few grams of carbohydrate in twenty-four hours.

Joslin³ in his recent monograph has given a table showing the distribution of the quotients in his series of severe cases. Curiously enough, his table for *all* the cases, both mild and severe, shows almost the same average quotients. This may be due to the fact that the carbohydrate in the diet was low, averaging less than one-quarter of the normal quota. One would naturally expect the respiratory quotients fourteen hours or so after food in milder diabetics to approach the normal average of about 0.82, but diabetics, even of the mildest type, seldom employ in their dietary the large excess of carbohydrate usually consumed by the normal man.

¹ Du Bois: *Endocrinology and Metabolism*, New York and London, D. Appleton & Co., 1922, 4, 95.

² Joslin: *Carnegie Institution of Washington Publication*, No. 323, 1923, p. 58.

³ Joslin: *Ibid.*, p. 167.

This excess in a normal man affects the quotient for many hours after the last meal, and basal quotients of between 0.82 and 0.90 are frequently observed. One practical point in the low quotients of diabetes is that, if we use the calorific value of oxygen for the average normal quotient of 0.82 in our calculations, the resulting figures for the basal metabolism will be about 2 per cent too high for a diabetic with a quotient of 0.73.

Abnormal Respiratory Quotients.—There are two groups of diabetic patients in which the respiratory quotient is unusual and puzzling. In the first group are the cases with a quotient below 0.71. Such abnormally low figures are found in severe diabetics who excrete part or all of the carbohydrate derived from the metabolism of protein. In the other group are the extremely undernourished diabetics who have unexpectedly high quotients many days after the last ingestion of enough carbohydrate to explain such high figures under normal conditions.

Low Quotients.—We shall consider first the abnormally low quotients found in the literature, selecting only the results obtained in laboratories in which the technic is known to be thoroughly good. We must remember, however, that even under the best conditions an error of 0.02 in the quotient may occur. For instance, even in the unusually good alcohol checks of the respiration calorimeter published by the Sage Institute in 1916, there are 2 quotients of 0.652 instead of the theoretical 0.667. In their alcohol checks published in 1917, there is 1 quotient as low as 0.640 and 1 as high as 0.682.

A respiratory quotient is of significance only because it enables us to estimate the percentage of calories being derived from the combustion of carbohydrate and the total grams of carbohydrate oxidized during the experimental period. If we fail to make these calculations, we miss the main point of the experiment. This has been emphasized by the work of Shaffer,¹ who has demonstrated that the whole question of acidosis depends on the proportion of calories derived from carbohydrate.

This calculation in diabetics who are excreting in the urine some or all of the glucose derived from protein is rather complicated. A thorough discussion of the chemical basis of

¹ Shaffer: *Jour. Biol. Chem.*, 1921, 47, 433, 449; 49, 143.

TABLE 54.—LOW RESPIRATORY QUOTIENTS IN THE LITERATURE.

Author.	Subject.	D : N	R. Q.	
			Total.	Non-prot.
Lusk ¹	Phlorhizinized dog	3.54	0.687	0.704
Benedict and Higgins ²	Healthy man, carbohydrate-free diet	..	0.67	
Lehmann and Zuntz ³	Fasting man	..	0.67	
Leo ⁴	Severe diabetic	..	0.66	
Magnus-Levy ⁵	Severe diabetic	..	0.654	
	Severe diabetic	..	0.637	
	Severe diabetic	..	0.651	
Leimdörfer ⁶	Severe diabetic	..	0.644	
	Severe diabetic	..	0.645	
	Severe diabetic	..	0.641	
	Severe diabetic	..	0.638	
Bernstein and Falta ⁷	Normal man carbohydrate-free diet	..	0.667	
Allen and Du Bois ⁸	G. S., severe diabetic	3.5	0.697	0.700
Geyelin and Du Bois ⁹	C. K., severe diabetic	3.97	0.687	0.699
McCann ¹⁰	Protein-fat meal after 8 days' fast	..	0.684	0.690
McCann and Hannon ¹¹	W. A.	..	0.700	0.693
	H. M.	..	0.677	0.663
	Diabetic soon after glucose or glycerol	..	0.667	0.657
Wilder, Boothby and Beeler ¹²	Bessie B., severe diabetic	3.68	0.68 to 0.71	0.640 to 0.70
Joslin ¹³	9 patients, severe diabetics	..	0.67+	
	37 observations after food	..	0.58 to 0.70	
Wilder and Winter ¹⁴	A-366687, epilepsy, fasting	..	0.69	
	A-376588, diabetes, mild infection	..	0.69	
	A-375561, diabetes, mild infection	..	0.66	
Benedict and Joslin ¹⁵	Normal man, H. L. H., protein-fat diet, Sept. 7	..	0.67	
	Normal man, H. H. A., protein-fat diet, Jan. 1	..	0.69	

¹ Lusk: Elements of the Science of Nutrition, third edition, Philadelphia and London, W. B. Saunders Company, 1919, p. 471.

² Benedict and Higgins: Am. Jour. Physiol., 1912, 30, 217.

³ Lehmann and Zuntz: Arch. f. path. Anat. u. Physiol., 1893, 131, Sup., 50.

⁴ Leo: Ztschr. f. klin. Med., 1891, 19, 101.

⁵ Magnus-Levy: Ztschr. f. klin. Med., 1905, 56, 83.

⁶ Leimdörfer: Biochem. Ztschr., 1912, 40, 328.

⁷ Bernstein and Falta: Deutsch. Arch. f. klin. Med., 1916-1917, 121, 95.

⁸ Allen and Du Bois: Clin. Cal. 17, Arch. Int. Med., 1916, 17, 1010-1059.

⁹ Geyelin and Du Bois: Jour. Am. Med. Assn., 1916, 66, 1532.

¹⁰ McCann: Proc. Soc. Exper. Biol. and Med., 1920, 17, 173.

¹¹ McCann and Hannon: Johns Hopkins Hosp. Bull., 1923, 34, 73.

¹² Wilder, Boothby and Beeler: Jour. Biol. Chem., 1922, 51, 311.

¹³ Joslin: Carnegie Institution of Washington Publication No. 323, 1923, 174.

¹⁴ Wilder and Winter: Jour. Biol. Chem., 1922, 52, 393.

¹⁵ Benedict and Joslin: Carnegie Institution of Washington Publication No. 176,

TABLE 55.—UNEXPECTEDLY HIGH RESPIRATORY QUOTIENTS IN SEVERE DIABETES.

Author.	Subject.	Calories from carbohydrate, per cent.	R. Q.	
			Total.	Non-prot.
Allen and Du Bois ¹	G. S., fasting 8 days, then carbohydrate-free diet (Nov. 23-Dec. 7, 1914)	2-15	0.727-0.759	0.712-0.753
Gephart, Aub, Du Bois and Lusk ²	C. K. (Dec. 22, 1915), 4 days' fast, 2 days' low-carbohydrate diet	6	0.734	0.728
	C. K. (Feb. 16, 1916), convalescent on liberal diet	62	0.915	0.972
Joslin ³	2 cases (1909-1913), negative carbohydrate balance	0.85-0.88	
	8 cases (1914-1917), positive carbohydrate balance	0.84-0.94	
	2 girls (1917), emaciated	0.84-0.91	
	Case No. 1011 (Nov. 23, 1917)	0.94	
Richardson and Mason ⁴	B. J., emaciated boy, aged 16 years.	0.79-0.91	
Richardson and Ladd ⁵	Fasting diabetics	0.72-0.78	
Holten ⁶	J. P. D.	0.92-0.97	

the various steps has been published by Lusk.⁷ By means of experiments on phlorhizinized dogs it has been shown that some of the amino-acids in protein are more or less completely convertible into sugar which is excreted in the urine. Chief among these are glycocoll, alanin, aspartic and glutamic acid. Others, such as leucin and lysin, do not form sugar. Our knowledge of the proportions of the various amino-acids in proteins is far from exact, and we must therefore allow a certain leeway for error in the following calculations:

For clinical purposes we can obtain results sufficiently exact by using the dextrose to nitrogen (D : N) ratio. This is obtained by placing a man or animal with severe diabetes on a diet which contains no carbohydrate. When the excre-

¹ Allen and Du Bois: Clin. Cal. 17, Arch. Int. Med., 1916, 17, 1010.

² Gephart, Aub, Du Bois and Lusk: Clin. Cal. 24, Arch. Int. Med., 1917, 19, 908.

³ Joslin: Carnegie Institution of Washington Publication No. 323, 1923.

⁴ Richardson and Mason: Jour. Biol. Chem., 1923, 57, 587.

⁵ Richardson and Ladd: Clin. Cal. 34, Jour. Biol. Chem., 1924, 58, 931.

⁶ Holten: The Respiratory Metabolism of Diabetics and the Influence of Insulin upon it. Copenhagen, Levin and Munksgaard, 1925.

⁷ Lusk: Clin. Cal. 8, Arch. Int. Med., 1915, 15, 939; Elements of the Science of Nutrition, Philadelphia, W. B. Saunders Company, 1919, p. 454.

tion of previously ingested carbohydrate has ceased the urine will contain sugar derived from the protein molecule and also the nitrogen substances from the same protein. Analysis of the urine for total nitrogen tells us the grams of protein metabolized; analysis for sugar tells how much carbohydrate has been derived from this protein. Minkowski¹ in 1893 found 2.8 grams of sugar for each gram of nitrogen (D:N :: 2.8:1) in the urine of depancreatized dogs. This indicated that 45 per cent of the protein was converted into sugar. A few years later Lusk and his collaborators found a D:N ratio of 3.65:1 in dogs injected with phlorhizin. This higher ratio indicates that 58 per cent of the protein can be converted into sugar. Mandel and Lusk² found this same ratio in a young man with severe diabetes and, realizing that it meant a complete loss of all power to oxidize carbohydrate, attached to such a ratio a bad prognosis.

All of our modern calculations in diabetes are now built upon the foundation of Lusk's D:N ratio of 3.65:1, as published in 1904. Its significance was almost entirely neglected by clinicians until the year of 1916. The partial list of ratios in the neighborhood of 3.65:1 given in Table 56 demonstrates rather impressively that such ratios are common and that they represent a complete or nearly complete loss of power to metabolize carbohydrate. This is shown in Fig. 12 (page 84) published by Du Bois⁴ in the Mayo Foundation Lectures. If we were not approaching a definite end point we should not find such a striking scarcity of ratios over 4:1. It is indeed surprising that there is not more of a scattering of the figures, since men and animals do not eliminate nitrogen and glucose quantitatively as it is formed. There is always some lag of nitrogen, and we cannot always be sure that some of the sugar excreted is not derived from carbohydrate stored in the body. These points have been emphasized by Joslin,³ who has never encountered D:N ratios as high as 3.65:1 in his own cases.

Grafe,⁵ in discussing this question, states that he does not

¹ Minkowski: Arch. f. exper. Pathol. u. Pharmacol., 1893, 31, 85.

² Mandel, A. R., and Lusk: Deutsch. Arch. f. klin. Med., 1904, 81, 472.

³ Joslin: Treatment of Diabetes Mellitus, third edition, Philadelphia and New York, Lea & Febiger, 1923, p. 243.

⁴ Du Bois: In Lectures on Nutrition, Mayo Foundation Lectures 1924-1925, Philadelphia and London, W. B. Saunders Company, 1925, 77.

⁵ Grafe: Ergeb. d. Physiol., 1923, 21, 346.

believe that the power to oxidize carbohydrate is necessarily lost completely, even in maximal diabetes. He qualifies this, however, by the statement that in maximal diabetes the oxidation of sugar is reduced to a minimum.

TABLE 56.—D : N RATIOS IN SEVERE DIABETES.

Author.	Case.	D : N.
Minkowski ¹	Depancreatized dogs	2.8
Reilly, Nolan and Lusk ²	Phlorhizinized dogs	3.75
Stiles and Lusk ³	Phlorhizinized dogs	3.65
Mandel and Lusk ⁴	Severe diabetes—medical student	3.65
Benedict and Lewis ⁵	Phlorhizinized man	3.68
Greenwald ⁶	Severe diabetes	3.66
Foster ⁷	Severe diabetes	3.4–3.6
Lusk ⁸	Mosenthal's diabetic	3.44–3.85
Allen and Du Bois ⁹	G. S., second day of fast	3.50
	G. S., 6th day of fast	1.55
	W. G., Jan. 15, 1915	3.8
	W. G., Jan. 22, 1915	3.12
	C. K., fasting	2.65–4.01
	J. D., protein diet	2.53–3.84
	J. R., severe diabetes	3.1–4.2
Murlin and Craver ¹²	D. M., severe diabetes	2.51–3.93
Christie ¹³	B. B., April 30 to May 4	2.96–3.98
Wilder, Boothby and Beeler ¹⁴	B. B., May 30 to June 2	3.39–3.84

A determination of the ratio is of service in estimating the severity of a case of diabetes and is an aid to the prognosis, although this is not invariably bad, even with a ratio of 3.65:1. In some patients the highest ratio occurs as a result of an infection (*e. g.* Cyril K.) and clears up in a few days. A thorough understanding of the significance of the ratio is of great importance in making us realize that protein is a source of sugar. This has been strikingly emphasized by Janney,¹⁵ who found that various food proteins yielded 40 to 80 per cent of glucose. Body proteins of man and experimental animals averaged about 58 per cent. He showed

¹ Minkowski: Arch. f. exper. Path. u. Pharmacol., 1893, **31**, 85.

² Reilly, Nolan and Lusk: Am. Jour. Physiol., 1898, **1**, 395.

³ Stiles and Lusk: Am. Jour. Physiol., 1904, **10**, 67.

⁴ Mandel, A. R., and Lusk: Deutsch. Arch. f. klin. Med., 1904, **81**, 479.

⁵ Benedict and Lewis: Proc. Soc. Exper. Biol. and Med., 1914, **11**, 134.

⁶ Greenwald: Jour. Biol. Chem., 1913, **16**, 375.

⁷ Foster: Deutsch. Arch. f. klin. Med., 1913, **110**, 501.

⁸ Lusk: Arch. Int. Med., 1912, **10**, 122.

⁹ Allen and Du Bois: Clin. Cal. 17, Arch. Int. Med., 1916, **17**, 1010.

¹⁰ Geyelin and Du Bois: Jour. Am. Med. Assn., 1916, **66**, 1532.

¹¹ Gephart, Aub, Du Bois and Lusk: Clin. Cal. 24, Arch. Int. Med., 1917, **19**, 908.

¹² Murlin and Craver: Jour. Biol. Chem., 1916, **28**, 301.

¹³ Christie: Jour. Am. Med. Assn., 1917, **68**, 170.

¹⁴ Wilder, Boothby and Beeler: Jour. Biol. Chem., 1922, **51**, 311.

¹⁵ Janney: Arch. Int. Med., 1916, **18**, 584.

for instance, that 100 grams of sanatogen, which contains 80.1 per cent protein and 4.2 per cent carbohydrate, yields 61 grams of glucose, the amount contained in 100 grams of bread. He warns against the pernicious use of proprietary diabetic foods which advertise their low carbohydrate percentages. As a matter of fact, it is the custom in some diabetic clinics to tabulate the "total available carbohydrate," adding to the carbohydrate ingested 58 per cent of the protein eaten or metabolized.

Bearing the facts in mind, it is not difficult to calculate the results of a respiration experiment made on a diabetic patient. If there is no glycosuria or if all the sugar of the urine is derived from ingested carbohydrate, the calculations are exactly the same as for normal persons. If, however, during an experimental period the patient has excreted glucose derived from protein, we must subtract an appropriate amount from the totals. Each gram of glucose represents a loss of 3.692 calories, 1.467 grams carbon dioxide and 1.067 grams oxygen. With a dextrose-nitrogen ratio of 3.65:1, 1 gram of nitrogen in the urine indicates the combustion of 6.25 grams of protein with the liberation of 26.51 - 13.47 calories ($3.65 \times 3.692 = 13.47$), 9.35 - 5.35 grams carbon dioxide, and the absorption of 8.45 - 3.89 grams oxygen.

TABLE 57.—PROTEIN RESPIRATORY QUOTIENT WITH D : N-3.65. (FROM LUSK).

	O ₂ , grams.	CO ₂ , grams.
Normal oxidation of 100 grams of beef protein . . .	138.18	152.17
Deduction for 16.28 \times 3.65 which corresponds to 59.41 grams glucose	63.38	87.15
R. Q. = 0.632	74.80	65.02

Converting the ratio of weights into the ratio of volumes, one finds that the respiratory quotient for proteins in complete diabetes is 0.632.

Since protein seldom furnishes more than 20 to 30 per cent of the calories in complete diabetes, it is obvious that the total respiratory quotient will be above 0.632 and will more nearly approach that of fat, 0.707. We must remember that the metabolism of fat is also abnormal and that large quantities of ketone bodies are being excreted instead of oxidized. Magnus-Levy¹ calculates that the maximal quantity of

¹ Magnus-Levy: Arch. f. Physiol., 1904, p. 379.

β -oxybutyric acid derivable from 100 grams of fat is 36 grams. This would reduce the quotient for fat from 0.707 to 0.669. Lusk points out that if this neutralized sodium bicarbonate, 15.23 grams of carbon dioxide would be eliminated and the respiratory quotient raised to 0.715. Other bases may be used, and it is obvious that we can make no exact allowances for the factor of ketosis.

There are several other elements which might affect our calculations. As the bicarbonate of the blood is neutralized by acids carbon dioxide is expelled. We must remember that when ammonia is converted into urea by union with carbon dioxide heat is absorbed in the reaction. In severe diabetes the excretion of ammonia is high and extra heat would be liberated in the body. Lusk calculated that in the severe diabetic, Cyril K., this additional heat did not exceed 1 calory an hour. Grafe¹ has calculated that if all the nitrogen from protein were eliminated as ammonia, the respiratory quotient would rise from the normal of 0.80 to 0.88. In the case of Cyril K. calculation shows that allowance for the ammonia would not change the quotient more than 0.01.

β -oxybutyric acid has a respiratory quotient of 0.889, but if sodium β -oxybutyrate were oxidized to bicarbonate of sodium, the quotient would be 0.667. Emery and Benedict² give the heat value of 1 gram of β -oxybutyric acid as 4.69 calories. Oxygen used in its oxidation has a heat value of 4.848 calories per liter. This is close to the heat value of a liter of oxygen used in the combustion of fat, 4.686, and also close to the value of 4.654, which is found when 100 grams of fat are partially oxidized, leaving 36 grams β -oxybutyric acid.

TABLE 58.—DIRECT AND INDIRECT CALORIMETRY IN SEVERE DIABETES.

Patient.	Date.	Total calories.	
		Indirect.	Direct.
G. S.	Nov. 9 to 16, 1914	672.7	658.4
J. D.	Nov. 15, 1915	112.2	108.1
C. K.	Dec. 15 to 22, 1915	924.0	944.9
		1708.9	1711.4
Difference			0.15%

¹ Grafe: *Ztschr. f. physiol. Chem.*, 1910, 56, 48.

² Emery and Benedict, F. G.: *Am. Jour. Physiol.*, 1911, 28, 301.

In the case of Cyril K., between December 15, 1915 and December 22, 1915, the only change from the usual calculation for normals was the allowance for the extra glucose excreted in the urine. In Table 58 we give the results of these calculations of the indirect calorimetry and compare them with the results obtained by direct calorimetry.

This close agreement indicates that there is no serious error in this calculation, but we must remember that differences of 2 to 3 per cent between the direct and indirect methods are found in some of the series of patients studied in the calorimeter, even in conditions where there are no disturbances of the metabolism.

We have not taken into account the effect of the conversion of the glycerol portion of the fat molecule into glucose. This constitutes about 10 per cent of fat by weight, and it is theoretically possible that it is all converted into sugar. Cremer¹ gave glycerol to phlorhizinized dogs and recovered 35 to 40 per cent of the weight of the glycerol as extra sugar in the urine. McCann, Hannon, Perlzweig and Tompkins² have obtained evidence that glycerol in diabetes is of value in reducing ketonuria. Just how much glycerol is converted into glucose in our severe diabetics we cannot say, but the amount is not great. For instance, Cyril K., on December 15, 1915 was oxidizing about 7 grams of fat an hour and this would contain 0.7 grams of glycerol.

It will appear from these calculations that we can account for practically all the very low quotients in the literature. The patient is living on a protein-fat basis and is excreting part or all of the glucose portion of the protein molecule. A slight additional depression of the quotient may possibly be due to the formation of β -oxybutyric acid from fat. There are still a few quotients in the literature slightly lower than we can account for, but it is not impossible that these are due to a technical error of ± 0.02 in the quotient that we have already mentioned. The conversion of the 10 per cent of glycerol contained in fat into carbohydrate, with subsequent excretion in the urine, would cause a slight depression in the quotient as calculated by Ringer. This is theoretically possible, and such a conversion has

¹ Cremer: München. med. Wchnschr., 1902, 49, 944.

² McCann, Hannon, Perlzweig and Tompkins: Arch. Int. Med., 1923, 32, 226.

been generally accepted in the last few years. There is no good evidence that in diabetes the remaining portion of the fat molecule is converted into sugar and excreted. If this really occurred we should find, in the reports of the best laboratories, many quotients below 0.67. The whole question of the possible transformation of fat into carbohydrate has recently been discussed by Lusk¹ who points out the slenderness of the evidence in support of the conversion of the fatty acid portion of the molecule into sugar. Meyerhof² has replied to this and we may hope that the scientific controversy will lead to new experiments which will help to clear up the uncertainties in this important phase of metabolism.

Krogh and Lindhard³ believe that with quotients over 0.90 carbohydrate is being transformed into fat, and with quotients below 0.80 sugar or substances allied to carbohydrate are formed from fat. No one can deny that this is theoretically possible. We can only say that, with quotients between 0.80 and 0.68 in diabetes, any possible sugar or carbohydrate-like substance formed from the fatty acid molecule is not excreted in the urine. It is either oxidized or stored, and if it be stored an equivalent amount of sugar from some other source is oxidized. Conversely, in normal men with quotients between 0.90 and 0.97, fat may be formed from carbohydrate, but it is either oxidized or stored, and if stored, an equal amount of fat from some other source is oxidized.

The question of the high quotients in severe diabetes is not so easily solved. There is no doubt but that many emaciated diabetics after long periods of starvation show quotients which indicate the combustion of considerable amounts of carbohydrate or similar substances which give high quotients.

Allen and Du Bois⁴ were puzzled by the high quotients shown by their subject, Gerald S., who, after fasting eight days and living for five days more on a carbohydrate-free diet, was, according to his quotient, deriving 2 per cent of his calories from the combustion of carbohydrate and, during the next two weeks on a similar diet, apparently derived from 10 to 15 per cent from carbohydrate. They calculated

¹ Lusk: *Biochem. Ztschr.*, 1925, 156, 334.

² Meyerhof: *Ibid.*, 1925, 158, 218.

³ Krogh and Lindhard: *Biochem. Jour.*, 1920, 14, 290.

⁴ Allen and Du Bois: *Clin. Cal. 17, Arch. Int. Med.*, 1916, 17, 1010.

that it would have required a previous storage of about 400 grams of glycogen in the body to account for the oxidation of this carbohydrate, and they believed such a storage improbable.

Joslin¹ has recently discussed this phenomenon without coming to any definite conclusion. He suggests two explanations as being worthy of further consideration. The first is the oxidation of the carbohydrate portion of the protein molecule with retention of the non-carbohydrate portion. He points out, however, that this would lead to an excessive retention of nitrogenous substances in the blood, with early death. The other possibility suggested by Joslin is the conversion of carbohydrate into fat. He has found that the few patients of the severe type whose experiments gave these high quotients were usually in extremis and without acidosis. He believes that "this precludes the explanation of the high respiratory quotient because, though this explanation would hold for a few days when the patient was free from acidosis, it would hardly explain the phenomenon for long periods when no evidence of acidosis exists."

Storage of Carbohydrates in Diabetes.—A more probable explanation for the high quotients found in certain emaciated diabetics has been given in the recent work of Richardson and Ladd.² They have shown that surprisingly large amounts of carbohydrate may be retained in the body of even a severely diabetic patient. (Fig. 52, p. 271).

Joslin³ has given an excellent discussion of the storage of carbohydrates in diabetes. He speaks of one of his patients who showed a positive carbohydrate balance of 520 grams when undergoing an oatmeal cure, although afterward, despite a rigorous diet, he never became sugar-free save for occasional days. It is quite probable that much of the apparent benefit from the oatmeal cure was due to a storage rather than to oxidation. Joslin has found a disappearance of levulose in severe diabetes. He quotes the literature showing that tissues removed from the livers of diabetic patients prove the presence of glycogen. In calculating the storage of sugar

¹ Joslin: *The Treatment of Diabetes Mellitus*, third edition, Philadelphia and New York, Lea & Febiger, 1923.

² Richardson and Ladd: *Clin. Cal.* 34, *Jour. Biol. Chem.*, 1924, 58, 931.

³ Joslin: *The Treatment of Diabetes Mellitus*, third edition, Philadelphia and New York, Lea & Febiger, 1923.

in the blood he is able to account for only 5 to 22 grams. Assuming that the other fluids of the body would contain the same percentage of sugar as the blood, he can account for the additional storage of 167 grams in the case of patients with high blood sugar (0.45 per cent).

High Nitrogen Excretion in Diabetes.—In diabetic patients, as in normal subjects, the ingestion of a large protein ration will be followed by a correspondingly high excretion of nitrogen. During fasting in both classes of individuals the excretion is usually moderate, seldom mounting much over 10 grams a day. This is due to the fact that both retain for a long time some of the fat deposits accumulated during years of plenty. Even the normal organism, if the fasting be prolonged, reaches a stage when the fat is almost exhausted and draws to a greater and greater extent upon his protein for an increasing share of the calories. This is called the "prelethal stage" of rising nitrogen excretion. During fever and various other toxic conditions there is an abnormally high nitrogen excretion due to a "toxic destruction of protein."

Certain well-studied diabetics in the literature have shown a high level of nitrogen elimination that cannot be ascribed to any mere washing out of residual nitrogenous end products stored in the body during the preceding days. There is every reason to believe that their protein metabolism is unusually high. One of the most striking examples is Cyril K.¹ Between December 14 and 17, 1915, he excreted between 35.3 and 38.3, grams of nitrogen a day, while his nitrogenous intake varied between 6.3 and 19 grams a day. McCann's² patient, W. A., on December 16 to 22, 1921, excreted 18.2 to 25.1 grams daily on a very low-protein intake. Joslin's patient No. 10111 on November 27 to 28, 1917, excreted 13.5 grams of nitrogen, with the low body weight of 26.3 kilograms. This woman's metabolism was extremely low, 785 calories a day, and she must have been deriving 46 per cent of the total heat from the metabolism of protein, a percentage reached by normal men only after an exceedingly large protein meal, as shown by the Sage investigators.³ The classical case of

¹ Geyelin and Du Bois: Jour. Am. Med. Assn., 1916, 66, 1532. Gephart, Aub, Du Bois and Lusk: Clin. Cal. 24, Arch. Int. Med., 1917, 19, 908.

² McCann, Hannon, Perlzweig and Tompkins: Arch. Int. Med., 1923, 32, 226.

³ Aub and Du Bois: Clin. Cal. 21, Arch. Int. Med., 1917, 19, 842.

Bessie B., described by Wilder, Boothby and Beeler,¹ on a protein intake of 103.6 grams a day, on May 1, 1921, excreted 17.86 grams of nitrogen. Estimating the total metabolism for this day as 1063 calories, she would have derived 45 per cent of them from protein if a large portion of the protein molecule had not been excreted as glucose. We see that Joslin's patient No. 1011, November 27 to 28, 1917, on a diet containing carbohydrate 10 grams, protein 40 grams, fat 27 grams, and alcohol 23 grams, was existing on as high a plane of protein metabolism as Bessie B. or the Sage dwarfs while they were digesting a meal of 660 grams of chopped beef, a meal so large that it required an hour of steady eating.

Joslin has for many years warned against a high-protein ration. The Sage investigators found their high D:N ratios and severest diabetes in Cyril K. after a diet containing 119 grams of protein, and in Joseph D. after suddenly increasing the protein ration from 94 to 156 grams a day. Wilder, Boothby and Beeler found the highest D:N ratio in the periods of highest protein ration. They conclude that

The sugar tolerance of the diabetic patient is depressed by high caloric, luxus diets, but more markedly depressed by protein than by isocaloric amounts of fat. This protein effect is not primarily due to the sugar and ketogenic substances, which the ingestion of protein throws on the metabolism, but to some other more specific action of protein the result of which is to interfere with the mechanism of sugar utilization,

A comparison of the figures obtained in the preceding cases should teach us to focus our attention not so much on the grams of nitrogen excreted as on the relationship of this figure to the level of the total metabolism. Joslin's patient No. 1011, emaciated and with very low metabolism, derived 46 per cent of her calories from protein when excreting nitrogen at the rate of 0.56 grams per hour. One of the normal controls in the Sage series² on May 18, 1914, excreted 0.53 grams of nitrogen an hour and derived only 19 to 20 per cent of his calories from protein because his heat production averaged 71.3 calories an hour instead of 32.7 calories an hour, as was the case with the poor diabetic. This simple arithmetic has been neglected by clinicians and investigators. The Sage investigators since 1915 have published for each calori-

¹ Wilder, Boothby and Beeler: *Jour. Biol. Chem.*, 1922, **51**, 311.

² Gephart and Du Bois: *Clin. Cal. 4, Arch. Int. Med.*, 1915, **15**, 835.

meter experiment the percentage of calories derived from protein, fat and carbohydrate, but these figures are never mentioned by others who discuss the papers.

Low Protein Metabolism in Diabetes.—As a result of the work outlined above, high-protein rations have been avoided in many clinics in this country during the last ten years. More recently on account of the writings of Newburgh and Marsh¹ and of Petrén of Lund, diets containing very small amounts of protein have been employed apparently with excellent clinical results. There does not seem to be anything abnormal in the nitrogen minimum of moderately severe diabetics. Lauter and Jenke² found the nitrogen minimum of 1.2 to 3.4 grams of urinary nitrogen a day while their normal controls excreted 1.8 to 3.4 grams per day. Per kilogram of body weight the figures were almost identical. Hannon³ and McClellan have been able to maintain a patient with moderately severe diabetes on nitrogen equilibrium for a long time at the low intake of 32 grams of protein a day. Further details of the diet on which they were able to accomplish this, will be awaited with interest.

Ketosis in Diabetes.—During the last few years there has been a brilliant solution of the problems of ketosis by Shaffer⁴ and Woodyatt.⁵ The reader is referred to their publications for the details, but a brief discussion of the question is necessary for a proper understanding of the basis of the modern treatment of diabetes.

Rosenfeld in⁶ 1885 said: "The fats burn in the fire of carbohydrate." This pithy statement was often quoted, although we did not realize how near it was to the truth. In 1910, Woodyatt⁷ suggested, on the basis of certain chemical studies, that the basis of antiketogenesis was a certain type of reaction in which one molecule of aceto-acetic acid would react with one molecule of an alcohol or glucose. Zeller,⁸ in 1914, studied normal individuals with low-protein diets, shifting

¹ Newburgh and Marsh: *Arch. Int. Med.*, 1920, **26**, 647. *Ibid.*, 1923, **31**, 455.

² Lauter and Jenke: *Deutsches Arch. f. klin. Med.*, 1925, **146**, 323.

³ Hannon and McClellan: *Proc. Soc. Exper. Biol. and Med.*, 1926, **23**, 817.

⁴ Shaffer, P. A.: *Jour. Biol. Chem.*, 1921, **47**, 433, 449; **49**, 143; 1922, **50**, xxvi; **54**, 399. *Physiol. Rev.*, 1923, **3**, 394.

⁵ Woodyatt: *Arch. Int. Med.*, 1921, **28**, 125.

⁶ Rosenfeld: *Deutsch. med. Wchnschr.*, 1885, **11**, 683.

⁷ Woodyatt: *Jour. Am. Med. Assn.*, 1910, **55**, 2109.

⁸ Zeller: *Arch. f. Physiol.*, 1914, p. 213.

the relative proportions of fat and carbohydrate. When the share of calories furnished by carbohydrate was changed from 25 to 10 per cent there was a slight rise in the nitrogen excretion and acetone appeared in the urine, increasing still farther as the carbohydrate ration was diminished. Lusk,¹ commenting on this experiment, called attention to the possibility that for the normal combustion of fat each molecule of β -oxybutyric acid, which is the end product of the oxidation of each fatty acid, requires the presence of a triose molecule. Ladd and Palmer² made similar observations on diabetics. All of the foregoing experiments contained a source of error that obscured the quantitative relationships. Lusk pointed out that Zeller assumed that the calories contained in the diet were liberated in metabolism. This, of course, follows only if the dietary mixture happens to match exactly the body's consumption of carbohydrate, fat and protein from exogenous and endogenous sources. This may occur in long experimental periods, but it frequently happens that for several days at a time there is a striking discrepancy between the substances fed and the substances metabolized.

Bearing this in mind, Shaffer and also Woodyatt, in 1921, made new calculations of much more exact nature. Shaffer³ was able to demonstrate in a test-tube that the simultaneous oxidation of glucose accelerated the oxidation of aceto-acetic acid. He then proceeded to analyze the various mixtures of foodstuffs metabolized by various fasting men, by Eskimos, and others on a high-fat, low-carbohydrate ration, and by Cyril K., the complete diabetic. On one side of the equation he placed the ketogenic molecules derived from the fatty acids of fat, since these are assumed to form an equimolecular amount of the keto acid. To these he added the ketones which can be produced from some of the amino-acids contained in meat, namely, leucine, phenylalanine and tyrosine. On the other side of the equation he placed the antiketogenic molecules derived chiefly from carbohydrate, but also in part from certain amino-acids and from the glycerol of fat. He found that, if the mixture of foodstuffs metabolized by the patient was such that the antiketogenic molecules (glu-

¹ Lusk: *Elements of the Science of Nutrition*, Philadelphia and London, W. B. Saunders Company, 1917, p. 271.

² Ladd and Palmer: *Proc. Soc. Exper. Biol. and Med.*, 1920-1921, 18, 109.

³ Shaffer: *Jour. Biol. Chem.*, 1921, 47, 433, 449.

cose or its derivative), equalled the ketogenic molecules, there was no significant increase in the ketones in the urine. If less than this proportion of glucose was metabolized the ketones in the urine increased above the normal limits.

TABLE 59.—EXAMPLES OF HIGH KETOSIS.

Author.	Case.	Excretion of β -oxy-butyric acid.
Magnus-Levy ¹		97.5
Gephart, Aub, Du Bois and Lusk ²	C. K., Dec. 15 to 17	77.8
Joslin ³	No. 740, Apr. 15 to 18	11.0-24.9
Mosenthal and Lewis ⁴	E. W., Dec. 3-10	50-111
Shaffer ⁵	K., Apr. 15 to 17	102-120
NON-DIABETIC SUBJECTS:		
Benedict ⁶	L., sixteenth to thirty-first days of fast	3.1-7.0
Means, Folin and Denis ⁷	Mrs. McK., obesity, fasting	17.3-18.5
Grafe ⁸	M. K., fasting in stupor	12.3-14.6
Bönniger and Mohr ⁹	"Schenk," fasting	17.6
Higgins, Peabody and Fitz ¹⁰	H. L. H., fourth day high fat	20.3
	F. W. P., fat diet	11.8
Landergren ¹¹	Normal men on low-carbohydrate diets	4.7-41.8

At the same time Woodyatt¹² was working out a formula expressed in somewhat different terms. The molecular weight of glucose is 180; the average of the molecular weights of oleic and palmitic acids is 270. The ration between the two is 1:1.5. We therefore have an equimolecular mixture if 1 gram of glucose is oxidizing at the same time as 1.5 grams of fatty acids.

Fat contains about 90 per cent of fatty acids. Protein furnishes about 44 per cent of its weight as fatty acids on

¹ Magnus-Levy: *Ergeb. d. inn. Med.*, 1908, **1**, 385.

² Gephart, Aub, Du Bois and Lusk: *Clin. Cal. 24, Arch. Int. Med.*, 1917, **19**, 908.

³ Joslin: *Diabetes Mellitus*, 3rd edition, Philadelphia, Lea & Febiger, 1923, p. 272.

⁴ Mosenthal and Lewis: *Bull. Johns Hopkins Hosp.*, 1917, **28**, 187.

⁵ Shaffer: *Jour. Biol. Chem.*, 1922, **54**, 399.

⁶ Benedict: *Carnegie Institution of Washington Publication No. 203*, 1915.

⁷ Means: *Jour. Med. Res.*, 1915, **32**, 121. Folin and Denis: *Jour. Biol. Chem.*, 1915, **21**, 183.

⁸ Grafe: *Ztschr. f. physiol. Chem.*, 1910, **65**, 21.

⁹ Bönniger and Mohr: *Ztschr. f. exper. Path. u. Therap.*, 1906, **3**, 675.

¹⁰ Higgins, Peabody and Fitz: *Jour. Med. Research*, 1916, **34**, 263.

¹¹ Landergren: *Nord. med. Arch.*, 1910, vol. **43**, Part 2, No. 10.

¹² Woodyatt: *Arch. Int. Med.*, 1921, **28**, 125.

account of the amino-acids which form aceto-acetic acid. These make up the ketogenic substances. Carbohydrate furnishes glucose roughly weight for weight. Protein gives 58 per cent of its weight as glucose. Fat probably gives 10 per cent of its weight as the glycerol is converted into glucose.

$$\frac{\text{Fatty acids}}{\text{Glucose}} = \frac{\text{FA}}{\text{G}} = \frac{0.44 \text{ P} + 0.9 \text{ F}}{\text{C} + 0.58 \text{ P} + 0.1 \text{ F}}$$

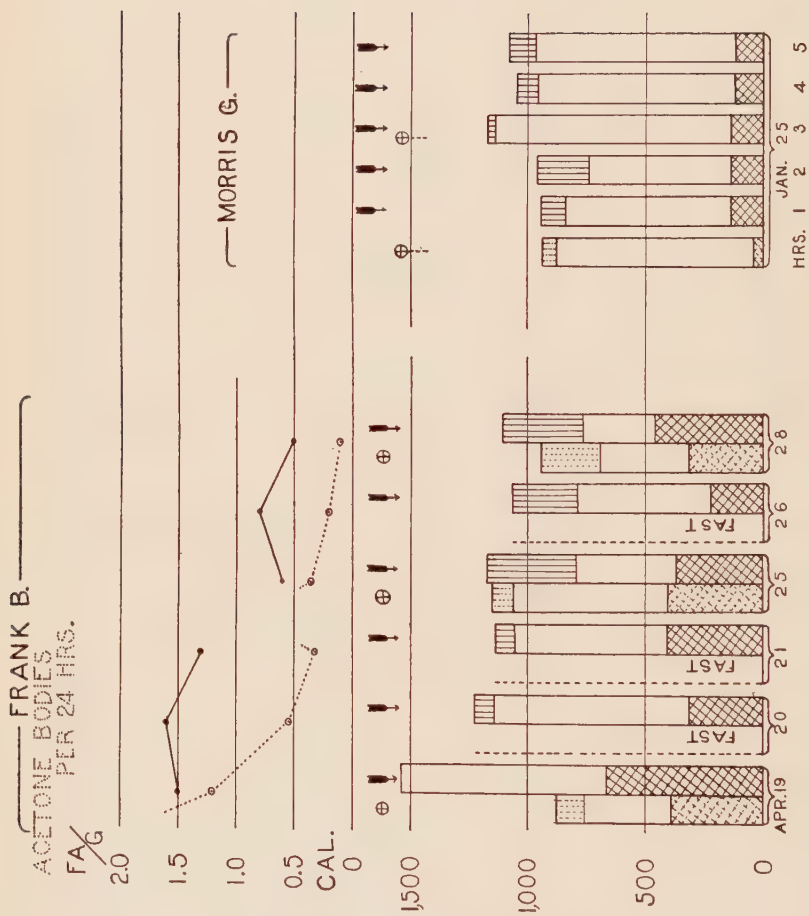
The initial ratio for acetonuria is $\frac{\text{FA}}{\text{G}} = \frac{1.5}{1}$. The initial ratio may be expressed as $\text{F} = 2\text{C} + 0.57\text{P}$ or for simplicity it is accurate enough to use $\text{F} = 2\text{C} \frac{\text{P}}{2}$. A metabolized mixture in which the grams of fat are equal to twice the grams of carbohydrate, plus one-half the grams of protein gives the largest proportion of fat that can be metabolized without an abnormal excretion of ketones.

Woodyatt used this method of calculation to give his diabetic patients the greatest number of calories without causing a ketosis and obtained good results, indicating the validity of the ratio.

Woodyatt and Shaffer therefore agreed that it required 1 molecule of glucose to help in the complete oxidation of 1 molecule of fat. Both recognized the inevitable errors in some of the calculations. Our clinical methods do not yet permit of exact values for the various substances formed from fat and protein. There is always a possibility of error in estimating the foods metabolized if we do not have the subject all day in a respiration chamber.

The customary method of reckoning the total metabolism is to make a basal test and add to this 10 per cent for the specific dynamic action of food and 10 to 50 per cent for muscular activity, this latter being largely guess work. We then determine the protein calories by multiplying the urinary nitrogen by 26.5 and estimate that the carbohydrate calories oxidized will be equal to the carbohydrate ingested. If we then subtract from the total calories the carbohydrate and protein calories, we have left the calories derived from fat. With so much guessing and assuming, the error may be considerable.

The general validity of the equimolecular ratio has been



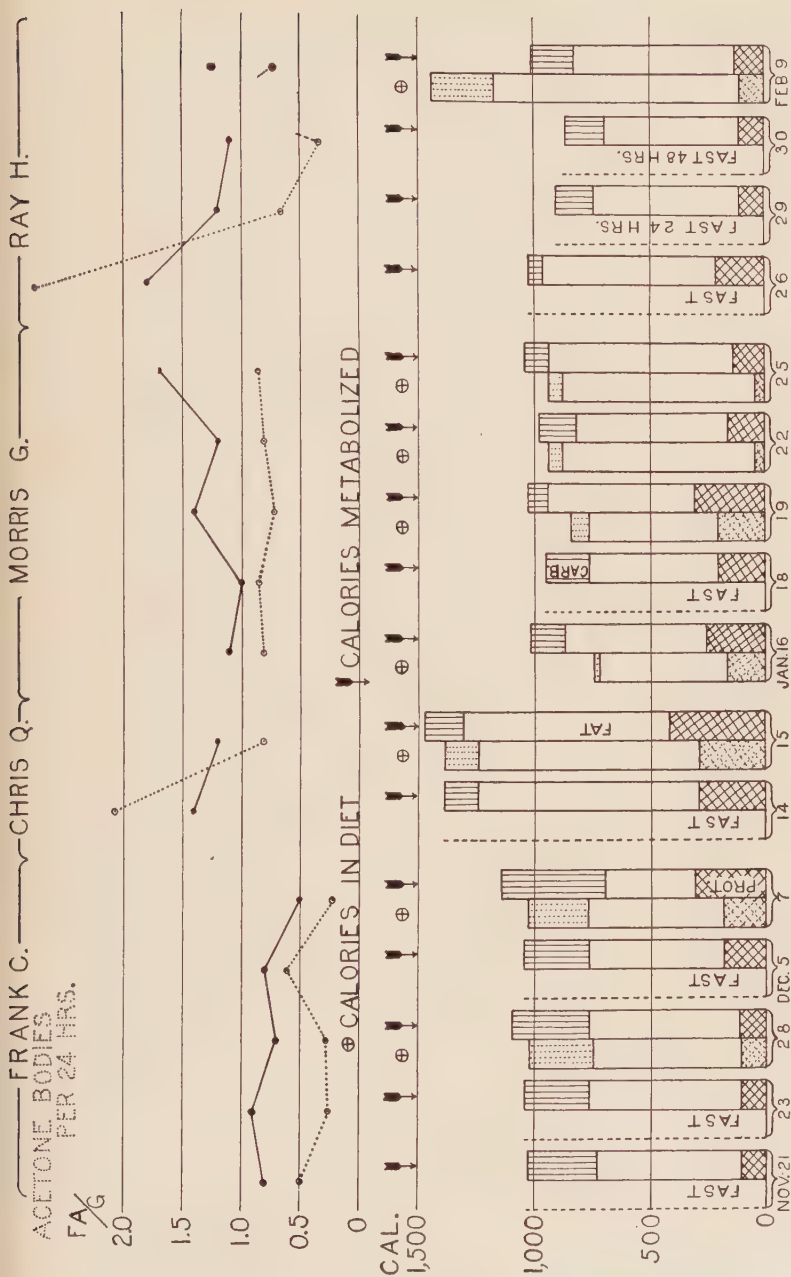


FIG. 51.—Showing the relation between the excretion of the acetone bodies on the fatty acid-glucose ratio, the diet and the foodstuffs oxidized. The total height of the columns represents the total calories of diet or metabolism. The cross-hatched portion at the bottom represents protein; the middle portion, which is blank, represents fat; the upper portion, vertically shaded, represents carbohydrate. The diet is marked by circles, and further, by broken shading. When no food was given the fact is indicated by the word "fast." The calories metabolized are designated by arrows. The curves drawn in solid lines represent the fatty acid-glucose ratio calculated from the calorimeter data. The broken lines represent the quantity of total acetone bodies as acetone in the twenty-four hour specimen of urine. (Richardson and Ladd.)

supported by the work of Hubbard and Wright¹ and by McCann, Hannon, Perlzweig and Tompkins,² although the latter authors state that frequently less than 1 molecule of glucose to 1 of fat will suffice to prevent acidosis.

Palmer and Ladd³ found that much higher proportions of fat could be given, and one of their patients, a hospital messenger, subsisted without acidosis for weeks on a diet containing 17 grams of carbohydrate, 50 of protein and 264 of fat.

Richardson and Ladd,⁴ in a series of well-planned and beautifully executed experiments, studied the relationship of the appearance and disappearance of ketosis to the proportions of carbohydrate and fat oxidized. Their initial ratios were all between 1.2 and 1.7, according to the Woodyatt formula, thus substantiating the view that 1 molecule of glucose is needed for the complete oxidation of 1 molecule of fatty acid. (Fig. 51.)

Wilson, Levine and Rivkin⁵ studied the question of ketosis and respiratory exchange in children by means of their carefully tested respiration chamber at the Nursery and Childs Hospital in New York. Using the same general experimental procedure that had been employed by Richardson and Ladd and Richardson and Levine,⁶ they found the threshold of ketosis consistently lower than in adults. Ketone bodies appeared in the urine with a fatty acid: glucose ratio as low as 1.0 which is the same as a molecular ratio of 0.7. The one patient that they studied with cyclic vomiting showed a tendency to oxidize less carbohydrate and more fat than the other children.

Shaffer⁷ made an exceedingly interesting study of the relationship of the respiratory quotient to ketosis. Since the level of the quotient depends almost entirely on the relationship of fat and carbohydrate burned, it must give an index of the ketogenic balance. We need not enter into

¹ Hubbard and Wright: *Jour. Biol. Chem.*, 1922, **50**, 361.

² McCann, Hannon, Perlzweig and Tompkins: *Arch. Int. Med.*, 1923, **32**, 226.

³ Palmer and Ladd: *Am. Jour. Med. Sci.*, 1923, **166**, 157.

⁴ Richardson and Ladd: *Clin. Cal.* 34, *Jour. Biol. Chem.*, 1924, **58**, 931.

⁵ Wilson, Levine and Rivkin: *Am. Jour. Dis. Child.*, 1926, **31**, 335.

⁶ Richardson and Levine: *Clin. Cal.* 39, *Exercise and the R. Q. in Diabetes*, *Jour. Biol. and Chem.*, 1925, **66**, 161.

⁷ Shaffer: *Jour. Biol. Chem.*, 1921, **49**, 143.

Shaffer's elaborate calculations, which led him to conclude that a total respiratory quotient of 0.76 shows the oxidation of equimolecular ketogenic and antiketogenic substances and constitutes the threshold of ketosis. It so happens that the percentage of protein makes little difference in the calculation since protein furnishes both ketogenic and antiketogenic substances, and the level of 0.76 holds good whether protein furnishes 10 or 25 per cent of the calories.

In this connection it is interesting to note that the 25 severe diabetics taken from the literature by Allen and Du Bois¹ had quotients below 0.78 and all except 1 showed acidosis. Joslin² gives a table of the respiratory quotients of his large series of patients. Most of those with high acidosis show quotients below 0.76 and most of those without acidosis are above 0.76, but there are many exceptions. Such exceptions are to be expected since the respiratory quotients may represent only a few minutes of the day, and the clinical estimations of acidosis depend on the observation of the patient during many days.

TABLE 60.—RELATIONSHIPS BETWEEN RESPIRATORY QUOTIENT, METABOLISM AND ACIDOSIS IN POSTABSORPTIVE EXPERIMENTS WITH DIABETICS BEFORE AND AFTER JUNE, 1914. (JOSLIN.)

Respiratory quotient and metabolism.	Number of experiments with all cases for respiratory quotient.							
	Before June, 1914, with acidosis.				After June, 1914, with acidosis.			
	0	+	++	+++	0	+	++	+++
0.64 to 0.69	6	10	..	2	5	3
0.70 to 0.75 . . .	8	9	31	34	10	25	57	11
0.76 to 0.79 . . .	9	2	6	5	25	21	36	2
0.80 to 0.83 . . .	2	..	2	..	36	20	14	1
0.84 to 0.90	1	2	..	27	6	6	
0.91 to 0.94	7			
Average respiratory quotient; all cases	0.76	0.75	0.73	0.72	0.81	0.77	0.76	0.72

This relationship of the respiratory quotient is brought out in the triangular graph constructed by the writer³ and

¹ Allen and Du Bois: Clin. Cal. 17, Arch. Int. Med., 1916, 17, 1010.

² Joslin: Carnegie Institution of Washington Publication No. 323, 1923, p. 190, Table 82.

³ Du Bois: Jour. Biol. Chem., 1924, 59, 43. (See p. 44.)

shown on page 44. In the lower left corner is the line which shows the threshold of ketosis according to the calculations of Shaffer and Woodyatt. All cases whose metabolism would be plotted to the left of this line should theoretically excrete some acetone bodies in the urine and the farther to the left, the greater the theoretical ketosis. It will be noted that no carbohydrate food is necessary to prevent ketosis if protein furnishes more than 44 per cent of the calories. This high-protein ration is dangerous in diabetes and is probably seldom attained in practice.

In 1922 Shaffer¹ reached the conclusion that each molecule of glucose is ketolytic for 2 molecules of aceto-acetic acid if there is a large excess of keto molecules. This is quite different from the threshold of ketosis. At the threshold there may be an uneven and unequal distribution of metabolites, so that it takes considerably more than the theoretical amount of total glucose to insure its reaction with every molecule of keto acid found in the body. Shaffer calculated the result in a large number of diabetic patients and normal men fasting or on low-carbohydrate rations and found ratios all the way from 1:1 to 2:1. The ratio of 2:1 indicates that each molecule of glucose will take care of 2 ketogenic molecules. Wilder and Winter,² in a careful study of 3 epileptic and 13 diabetic patients, found ratios between 1.2:1 and 2:1. They believe that it is wise in planning diets to allow only such food mixtures as will avoid the 2:1 ratio by a safe margin.

The question is not yet settled, and we are in doubt as to the exact molecular ratios in the chemical reaction. All that we can say is that, with an excess of keto acids in the body, 1 oxidizing molecule of glucose can aid in the complete combustion of about 2 molecules of fatty acid, and that when the keto acids are present in small amounts, it seems to require about 2 molecules of glucose for 2 of fatty acid. In planning our diets we therefore must use a ratio of 1:1 ($\frac{\text{FA}}{\text{G}} = 1.5$) to prevent ketosis completely, but we can get along with about one-half this amount of total available glucose if we have a low-carbohydrate tolerance and are obliged to put up with a moderate formation of ketones.

¹ Shaffer: *Jour. Biol. Chem.*, 1922, **50**, xxvi; **54**, 399.

² Wilder and Winter: *Jour. Biol. Chem.*, 1922, **52**, 393.

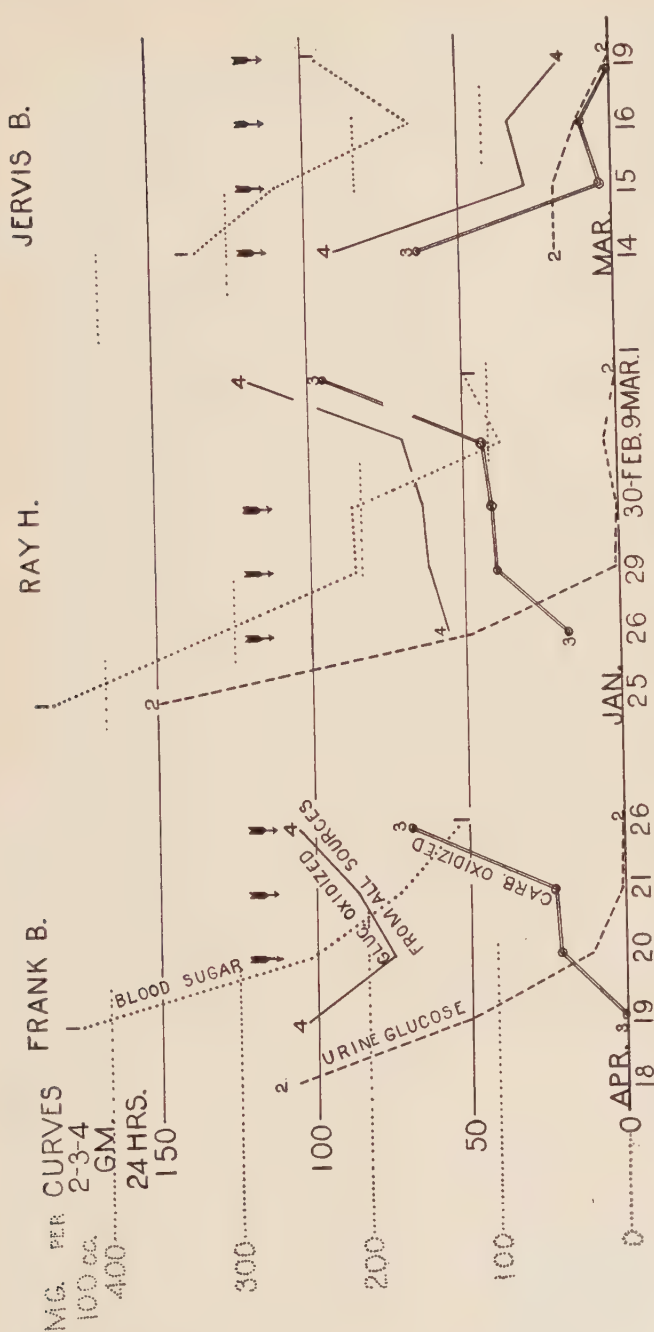


FIG. 52.—The effect of fasting on the metabolism of glucose. Curve 1 represents blood sugar; Curve 2, glucose in the urine in grams in twenty-four hours; Curve 3, carbohydrate oxidized, not including the glucose from protein and fat, calculated from the calorimeter data and expressed in grams per twenty-four hours; Curve 4, oxidation of glucose derived from all sources, including protein and the glycerol of the fat, calculated from the calorimeter data by means of the formula of Woodyatt, and expressed in grams per twenty-four hours. The arrows point to observations on patients without food. Note that the first two patients show an increase in the total grams of glucose oxidized during fasting. (Richardson and Ladd.)

Fortunately, at the present date we can increase the oxidation of carbohydrates by means of insulin. In the old days we cut the suit to fit the cloth. This often made a scant garment. Sometimes we substituted sackcloth and ashes which did more harm than good. Sometimes we left the customer naked for weeks at a time. Nowadays we can order more cloth from the manufacturer.

The Effect of Food on the Metabolism in Diabetes.—In mild diabetes there is every indication that the effects of food are the same as in health. Even in severe diabetes the specific dynamic action of most foods appears to be approximately normal. It was recognized at an early date that the administration of carbohydrate could only push the respiratory quotient up to a certain level and that an excess of carbohydrate above the limit of tolerance was excreted and not oxidized. This is in accord with our modern views that the pancreas is able to elaborate in diabetes a rather strictly limited amount of insulin and that the amount of insulin formed has a quantitative relationship to the amount of sugar that can be oxidized. We must remember, however, that the carbohydrate tolerance is not always absolutely fixed for a given patient but can vary under different influences. Increased amounts of protein in the food will cause increased protein metabolism, but Richardson and Mason¹ have conclusively shown that in emaciated diabetics an increase in the fat of the diet is often followed by fat storage without increased fat combustion. At one time von Noorden advocated the use of a large amount of oatmeal combined with occasional fast days in the treatment of diabetes. This stimulated a considerable amount of work on the effect of various carbohydrates in raising the respiratory quotient. Benedict and Joslin² concluded that the carbohydrate ingested produced no effect on the metabolism. Joslin³ showed the failure of either oatmeal or potato to raise the respiratory quotient notwithstanding positive carbohydrate balances as high as 100 grams. Falta⁴ gave a diabetic 400 grams of oatmeal daily and found no rise in the quotient until the

¹ Richardson and Mason: *Clin. Cal.* 33, *Jour. Biol. Chem.*, 1923, **57**, 587.

² Benedict, F. G., and Joslin: *Carnegie Institution of Washington Publication* No. 136, 1910; No. 176, 1912.

³ Joslin: *Arch. Int. Med.*, 1915, **16**, 693.

⁴ Falta: *Med. Klin.*, 1914, **10**, 9.

third day. Rolly¹ and Roth² found no appreciable change in the quotients after administration of different carbohydrates to diabetics. Allen and Du Bois³ studied a patient with moderately severe diabetes whose basal respiratory quotients were 0.75 and 0.79. After giving large amounts of bread or oatmeal for three days the quotients were only 0.82 and 0.81.

Benedict and Joslin⁴ studied a few patients after food in 1910, and Joslin⁵ published some excellent illustrative protocols in his book. For a store-house of information one should consult his recent monograph⁶ which gives the details of an enormous number of experiments. He observed increases of metabolism of 10 to 25 per cent after various sugars and other foodstuffs. In some cases the respiratory quotients rose and in others fell. Often it was practically unaffected.

The results following the ingestion of levulose by patients with severe diabetes were puzzling. It produced a greater rise in heat production than in the experiments with normal men or mild diabetes. It was apparently well utilized, although some was excreted in the urine. The respiratory quotient rose during the first two hours and then fell below the basal level. Joslin believes that there was an oxidation of the substance. We note, however, that the fall in the quotients after the second hour more than counterbalances the early rise. This suggests some reversible chemical reaction going first in one direction and then in the other. A similar but briefer fluctuation in quotients is found during and after deep breathing (*Auspumpung*). In a few of Joslin's diabetics the respiratory quotient rose higher than 1, indicating a conversion of carbohydrate into fat. He suggests that the conversion may take place at even lower levels of the quotient. Boothby and Sandiford⁷ point out that such a conversion appears to be contrary to the evidence of quantitative studies of the carbohydrate balance in diabetes.

¹ Rolly: Deutsch. Arch. klin. Med., 1912, 105, 494.

² Roth: Wiener klin. Wchnschr., 1912, 25, 1864.

³ Allen and Du Bois: Clin. Cal., Arch. Int. Med., 1916, 17, 1010.

⁴ Benedict, F. G., and Joslin: Carnegie Institution of Washington Publication No. 136, 1910.

⁵ Joslin: The Treatment of Diabetes Mellitus, third edition, p. 542, Philadelphia and New York, Lea & Febiger, 1923.

⁶ Joslin: Carnegie Institution of Washington Publication No. 323, 1923.

⁷ Boothby and Sandiford: Physiol. Rev., 1924, 4, 69.

Orange juice was found to give about the same results as levulose. The composition of a group of California oranges is quoted by Joslin as follows:

Sucrose	4.9 to 5.4 per cent
Fruit sugars (dextrose and levulose)	4.4 to 6.8 "
Citric acid (respiratory quotient, 1.33) . . .	1.3 to 1.5 "

Glucose does not seem to cause as sharp a rise in the quotient as levulose. Wilder, Boothby and Beeler¹ had found a depression of quotient in Bessie B. after mixed food and after glucose. McCann and Hannon,² studying the effects of glucose on diabetic patients, found some in whom it caused a rise similar to that found in normal persons. Curiously enough, these patients did not respond well to treatment. In a group of patients who later did respond to treatment they found that glucose caused an actual fall in the quotient for an hour or so. Glycerol caused a similar effect. McCann³ had noted a depression of quotient after giving protein to a normal man who had fasted eight days. Benedict and Joslin⁴ gave at 12.12 P.M. 582 grams of cooked oatmeal to a man who had been on a carbohydrate-free diet for five days. The average respiratory quotient before the oatmeal was 0.69. At 12.41 the quotient was 0.67; at 1.08 P.M. 0.70. The highest point reached was only 0.74. On the next day 100 grams of cane sugar raised the quotient to 1.04.

Benedict and Carpenter⁵ in 1918 reported a large number of experiments on normal subjects after giving 100 grams of various sugars. The ingestion of dextrose was followed by a transient fall in quotient in one-half of the cases, the phenomenon being most marked in 2 subjects who had recently been living on a carbohydrate-free diet. A similar temporary decrease occurred in 2 out of 5 experiments with lactose, but was never seen after levulose or sucrose. Wilder, Boothby Barborka, Kitchen and Adams⁶ found a similar fall in quotient in diabetes after giving dextrose both with and without

¹ Wilder, Boothby and Beeler: *Jour. Biol. Chem.*, 1922, **51**, 311.

² McCann and Hannon: *Johns Hopkins Hosp. Bull.*, 1923, **34**, 73.

³ McCann: *Proc. Soc. Exper. Biol. and Med.*, 1920, **17**, 173.

⁴ Benedict, F. G., and Joslin: *Carnegie Institution of Washington Publication No. 176*, 1912, p. 131.

⁵ Benedict and Carpenter: *Ibid.*, No. 261, 1918, p. 241.

⁶ Wilder, Boothby, Barborka, Kitchen and Adams: *Jour. Metab. Res.*, 1922, **2**, 701.

insulin. The existence of this phenomenon is now well established. Its cause is unknown.

This makes it very difficult to estimate the combustion of a foodstuff given to a diabetic patient. Our normal controls have usually been on mixed diets, and they still have a plentiful supply of glycogen in the liver when food experiments are made. The diabetics have usually been on low-carbohydrate diets, and their glycogen reserves are presumably low. Some of the diabetics have rather high destruction of their own body protein which may be temporarily increased or diminished by the food administered. Their blood sugar is normally high, and their oxidative power for carbohydrate low. It is not fair to compare them with normal controls unless the controls have been given a diabetic diet for several days. Even then we cannot reproduce the high blood sugar.

If, therefore, it is difficult to derive from the oxygen consumption and respiratory quotient the exact combustion of such simple substances as glucose and levulose, how much more difficult must it be to obtain information regarding glycerol (respiratory quotient 0.86) and alcohol (respiratory quotient 0.666).

McCann and Hannon¹ obtained some evidence of favorable effects of glycerol, calcium hexose phosphate and calcium glycerophosphate. Allen and Du Bois² studied the effects of alcohol on a diabetic in the calorimeter. The respiratory quotient rose and then fell. The authors were at a loss to tell whether this was due to vasomotor or respiratory changes or increased carbohydrate metabolism or combustion of acetone bodies mixed with the combustion of alcohol.

Joslin³ reports a few experiments on diabetics after the ingestion of protein alone and a number of tests made after mixed meals. Wilder, Boothby and Beeler⁴ also made observations after mixed meals. It is difficult to find out much from the respiratory quotient, since this would not change appreciably from its basal level if the protein or food mixtures were all oxidized. Both Joslin and the Mayo Clinic investigators obtained rises of 10 to 30 per cent in metabolism, and this specific dynamic action does not seem to be different

¹ McCann and Hannon: *Johns Hopkins Hosp. Bull.*, 1923, **34**, 73.

² Allen and Du Bois: *Clin. Cal.* **17**, *Arch. Int. Med.*, 1916, **17**, 1010.

³ Joslin: *Carnegie Institution of Washington Publication No.* 323, 1923.

⁴ Wilder, Boothby and Beeler: *Jour. Biol. Chem.*, 1922, **51**, 311.

from that which would be found in normal persons. On the other hand, Richardson and Mason¹ were able to give considerable amounts of food without increasing the metabolism more than 2 to 3 per cent. They placed the patient in the calorimeter fasting and found out how many grams of protein, fat and carbohydrate he was consuming each two-hour period. Then they gave him at two-hour intervals exactly the same amounts of the three foodstuffs. This they called a "replacement diet."

The Effect of Exercise in Diabetes.—We have neglected the study of exercise in diabetes. Only a few of our patients are motionless during the day time. Most of them are leading sedentary lives. A few are extremely active. What effect has exercise upon the carbohydrate combustion? We know that it increases total metabolism. If it does not also increase carbohydrate metabolism it must be extremely dangerous in cases of severe diabetes when the limited oxidation of anti-ketogenic substances is just able to check the ketosis as long as the patient is quiet.

Clinical observation gives us no clear-cut answer. Most severe cases are too weak to attempt to do much. Some do badly if they exercise; some can walk long distances with apparent benefit. Allen² found an increase in carbohydrate tolerance and improvement in general condition when his undernourished patients took vigorous exercise. He also reported that diabetic dogs which showed glycosuria while taking 100 grams of bread were able on exercising to take 200 grams daily without glycosuria.

Nehring and Schmoll³ in 1907 found that it was possible to reduce the sugar excretion of diabetics by controlling the muscular activity. Mohr⁴ obtained in a diabetic dog a rise in quotient from 0.708 to 0.837 when the dog used the treadmill. It is reported by von Noorden⁵ that Salomon found a decrease in the quotient when 2 patients with severe diabetes performed heavy work. Benedict and Joslin⁶ found a slight

¹ Richardson and Mason: Clin. Cal. 33, Jour. Biol. Chem., 1923, 57, 587.

² Allen: Boston Med. and Surg. Jour., 1915, 173, 743.

³ Nehring and Schmoll: Ztschr. f. klin. Med., 1897, 31, 59.

⁴ Mohr: Ztschr. f. exper. Pathol. u. Therap., 1907, 4, 939.

⁵ von Noorden: Metabolism and Practical Medicine, Chicago, W. T. Keener & Co., 1907, 3, 542.

⁶ Benedict and Joslin: Carnegie Institution of Washington Publication No. 136, 1910, p. 217.

increase in quotient when a diabetic increased moderately his oxygen consumption by twitching his muscles. Allen and Du Bois¹ found a similar slight increase in 1 case studied. Grafe and Salomon² made an important contribution by studying a number of diabetics. They noted during severe exercise on an ergostat a fall in the quotient, but a total rise in the amount of sugar oxidized. Richardson and Levine³ have confirmed this employing moderate exercise in the Sage calorimeter.

TABLE 61.—EXPERIMENTS SHOWING THE EFFECT OF WORK ON METABOLISM IN DIABETES. (GRAFE.)

Type of diabetes.	Respiratory quotient before work.	Respiratory quotient during work.	Change in respiratory quotient.	Metabolism rise during work, per cent.	Carbohydrate combustion per hour before work, gm.	Carbohydrate combustion per hour during work, gm.	Change in carbohydrate combustion, per cent.
Moderately severe; no acidosis	0.777	0.764	-0.013	83.	2.95	4.32	+47
Moderately severe; beginning acidosis	0.800	0.757	-0.047	171.	4.13	4.86	+18
Moderately severe; beginning acidosis	0.836	0.793	-0.043	134.1	3.95	6.08	+54
Rather severe	0.755	0.711	-0.044	54.1	2.23	0	-
Rather severe	0.777	0.732	-0.045	218.1	3.60	3.690	+ 2.5
Pancreas diabetes after acute pancreatitis	0.732	0.736	+0.004	117.9	1.246	1.685	+35.3
Moderately severe at first with acidosis	0.730	0.723	-0.007	95.8	0.957	0.750	-21.6
Moderately severe at first with acidosis	0.793	0.775	+0.018	139.1	2.93	5.425	+85.6
Moderately severe with very low tolerance	0.717	0.710	-0.007	58.9	Tr.	0	-

It is well to remember, therefore, that a glucose tolerance established at a resting level may be changed if the patient exercises. Though the carbohydrate oxidation may increase somewhat, it may not keep pace with the increased oxidation of fatty acid molecules.

The Effect of Insulin on the Respiratory Metabolism in Diabetes.

—The discovery of insulin by Banting and Best⁴ was rapidly

¹ Allen and Du Bois: Clin. Cal. 17, Arch. Int. Med., 1916, 17, 1010.

² Grafe and Salomon: Deutsch. Arch. f. klin. Med., 1922, 139, 369.

³ Richardson and Levine: Jour. Biol. Chem., 1925, 66, 161.

⁴ Banting and Best: Jour. Lab. and Clin. Med., 1922, 7, 251, 464.

followed by a voluminous literature on the subject. The reader is referred to the bibliography, complete up to April, 1923, given in the *Journal of the American Medical Association*¹ for the details and clinical applications. Only a few of the papers dealing with the effect of this substance on the respiratory exchanges are discussed in this place.

It must be remembered that previous investigators had obtained promising results with pancreatic extracts but had abandoned the investigations. Murlin and Kramer² secured a slight rise of respiratory quotient in a dog by the administration of a combined extract of pancreas and duodenal mucosa. In 2 other dogs this caused a diminution of the urinary sugar. They did not feel sure that these slight changes indicated an increased combustion of carbohydrate. Murlin did not drop the problem and he had resumed work on pancreatic extracts in 1921 at about the same time that Banting and Best began their successful investigations.

Banting, Best, Collip and Macleod,³ in one of their earliest papers on insulin, reported that it caused very definite rise in the respiratory quotient of animals that responded only slightly to sucrose alone. In this same paper they showed that insulin decreased the blood sugar, urinary sugar, and ketosis, thus proving that it caused an actual increase in the oxidation of glucose. Subsequent work by other investigators has merely established these facts more definitely. Thus, Joslin, Gray and Root,⁴ studying human subjects, found after insulin and food that the respiratory quotient sometimes rose above 1. In a series of 11 patients under insulin treatment the basal metabolism showed an average rise of 9 per cent. Wilder, Boothby, Barborka, Kitchen and Adams⁵ found a sharp rise in heat production and respiratory quotient after giving levulose with insulin. After glucose and insulin there was a sharp rise in heat production but an initial fall in quotient, just as in normal subjects and in diabetics without insulin. With insulin, however, the initial fall was followed by a distinct rise in quotient above the basal level.

¹ Banting, Best, Macleod, *et al.*: Jour. Am. Med. Assn., 1923, 80, 1241.

² Murlin and Kramer: Jour. Biol. Chem., 1913, 15, 365.

³ Banting, Best, Collip and Macleod: Trans. Roy. Soc. Canada, 1922, vol. 16, Sect. V.

⁴ Joslin, Gray and Root: Jour. Metab. Res., 1922, 2, 651.

⁵ Wilder, Boothby, Barborka, Kitchen and Adams: Jour. Metab. Res., 1922, 2, 701.

Fitz, Murphy and Grant,¹ in the same issue as the two previous papers, reported a rise in quotient and found that it sometimes remained elevated for three days following the withdrawal of insulin. They reported a distinct rise in total metabolism but did not believe that insulin had any effect on basal metabolism except indirectly.

Lyman, Nicholls and McCann² studied the respiratory exchanges after epinephrin and after insulin on normal subjects and diabetics. Epinephrin caused in normals a sharp rise in quotient and heat production and blood sugar. With diabetics the rise in quotient and blood sugar was much less striking. The drug changed the rate of alveolar ventilation, and the authors did not believe that the rise in quotient after epinephrin proved an increased oxidation. Insulin caused a rise of quotient in normals and diabetics, but three of the diabetics showed a transient fall in quotient. The effects of insulin have been exceedingly well discussed in the reviews by McCann³ and Boothby and Sandiford.⁴

Application of Metabolism Studies to the Treatment of Diabetes Mellitus.—We have passed through many phases in our treatment of diabetes. Our improvements have taken place when we have realized the significance of certain laws of metabolism which have been known but not appreciated for years. Our mistakes have been due to our neglect of these laws. At the present time we believe that our method of treatment is rational and satisfactory, but only the future can tell us what important facts we have overlooked.

The diet of Naunyn consisted in liberal amounts of protein and fat and small amounts of carbohydrate. Its chief fault seems to have been that it contained too much protein and too many calories. It did not tend to reduce the basal metabolism. The Allen fasting treatment was successful chiefly because it diminished the need for calories and allowed the patient to exist on a lower metabolic plane. At the present time we believe that the restriction was unnecessarily severe and that the harmful effect of fat was overrated. Newburgh and Marsh perhaps went to the other extreme when they gave large

¹ Fitz, Murphy and Grant: *Jour. Metab. Res.*, 1922, 2, 753.

² Lyman, Nicholls and McCann: *Jour. Pharm. and Exper. Therap.*, 1923, 21, 343.

³ McCann: *Calorimetry in Medicine*, Williams Wilkins Company, Baltimore, 1924. (Also in *Medicine*, 1924, 3, 1.)

⁴ Boothby and Sandiford: *Physiol. Rev.*, 1924, 4, 69.

amounts of fat. It seems, however, that this did not increase materially the fat oxidation, since it replaced the body fat which was being consumed. The excess was stored.

Our modern treatment is well described by Woodyatt,¹ Wilder,² Shaffer,³ and Hannon and McCann.⁴ Of course in mild cases it is only necessary to reduce the carbohydrates in the diet to a point which relieves the glycosuria and hyperglycemia. If the patient is too stout his weight should be reduced. As a rule there is no ketosis, since this can be avoided by amounts of carbohydrate much smaller than the total usually consumed by normal men. We must, of course, remember that every mild diabetic is potentially a severe case, especially during an attack of an infectious disease.

In severe cases the diet must be carefully planned. The patient has a greatly diminished power to oxidize glucose derived from protein and glycerol as well as carbohydrate food. The carbohydrate tolerance is usually fairly definitely fixed at a certain level and cannot be increased except by insulin. The basal metabolism is also more or less fixed, especially if it has been already reduced to a low level. The protein metabolism can be reduced until it furnishes about 10 per cent of the total calories and perhaps a little less. Fat must furnish all the calories not supplied by protein or carbohydrate. Either food fat or body fat may be utilized.

Woodyatt⁵ first emphasized that the rationale of dietetic management in diabetes is to bring the quantity of glucose entering the metabolism from all sources below the quantity that can be utilized without abnormal waste, and to adjust the supply of ketogenic bodies in relationship to the quantity of glucose so that, in the mixture of foodstuffs oxidizing in the tissues, the ratio of ketogenic bodies to glucose shall not exceed the limits compatible with freedom from ketonuria. He calculates the ketogenic-antiketogenic ratio $\left(\frac{FA}{G}\right)$ in grams, as follows:

¹ Woodyatt: *Endocrinology and Metabolism*, New York and London, D. Appleton & Co., 1922, 4, 280.

² Wilder: *Jour. Am. Med. Assn.*, 1922, 78, 1878.

³ Shaffer: *Jour. Biol. Chem.*, 1922, 54, 399.

⁴ Hannon and McCann: *Johns Hopkins Hosp. Bull.*, 1922, 33, 128.

⁵ Woodyatt: *Arch. Int. Med.*, 1921, 28, 125; *Endocrinology and Metabolism*, New York and London, D. Appleton & Co., 1922, 4, 281.

$$\frac{0.44 \text{ Protein} + 0.9 \text{ Fat}}{\text{Carbohydrate} + 0.58 \text{ Protein} + 0.1 \text{ Fat}}$$

If the total amount of fatty acids divided by the total amount of glucose gives a figure of 1.5 or less there will be no significant ketosis. The combination which will give a ratio of 1.5 can be simplified with slight loss of accuracy to

$$\text{Fat} = 2 \text{ Carbohydrate} + \frac{\text{Protein}}{2}$$

Woodyatt emphasizes the fact that we must consider the materials metabolized in the body, not merely those given in the diet. He does not believe that fasting is rational unless it is needed to improve the general condition, and he points out that it is possible to maintain the normal body with a diet that contains but 10 per cent more calories than are produced in fasting.

Woodyatt discusses a series of hypothetical diets. His figures in Table 62 speak for themselves.

TABLE 62.

Diet.	I.	II.	III.	IV.
Carbohydrate	10	77	60	51
Fat	84	108	91	135
Protein	150	30	85	70
		<hr/>	<hr/>	<hr/>
Total available glucose	105	105	118	105
Total calories	1400	1400	1400	1700
FA				
<hr/> G	1.35	1.05	1.01	1.45

Hannon and McCann¹ use Woodyatt's $\frac{\text{FA}}{\text{G}}$ ratio of 1.5 but estimate the total metabolism from actual basal determinations plus an allowance of 10 per cent for the specific dynamic action of food and muscular activity. If metabolism tests have not been made, they estimate the metabolism from the surface area. Instead of giving protein arbitrarily at 1 gram per kilogram of body weight they use a rather more rational method of giving enough to furnish a certain desired percentage of the calories. They have constructed a graph which

¹ Hannon and McCann: Johns Hopkins Hosp. Bull., 1922, 33, 128. McCann, Hannon, Perlzweig and Tompkins: Arch. Int. Med., 1923, 32, 226.

makes it possible in a few seconds to plot out the diet which furnishes the desired number of calories and the proper percentage of protein with the minimal amount of carbohydrate and maximal amount of fat that will avoid ketosis. They

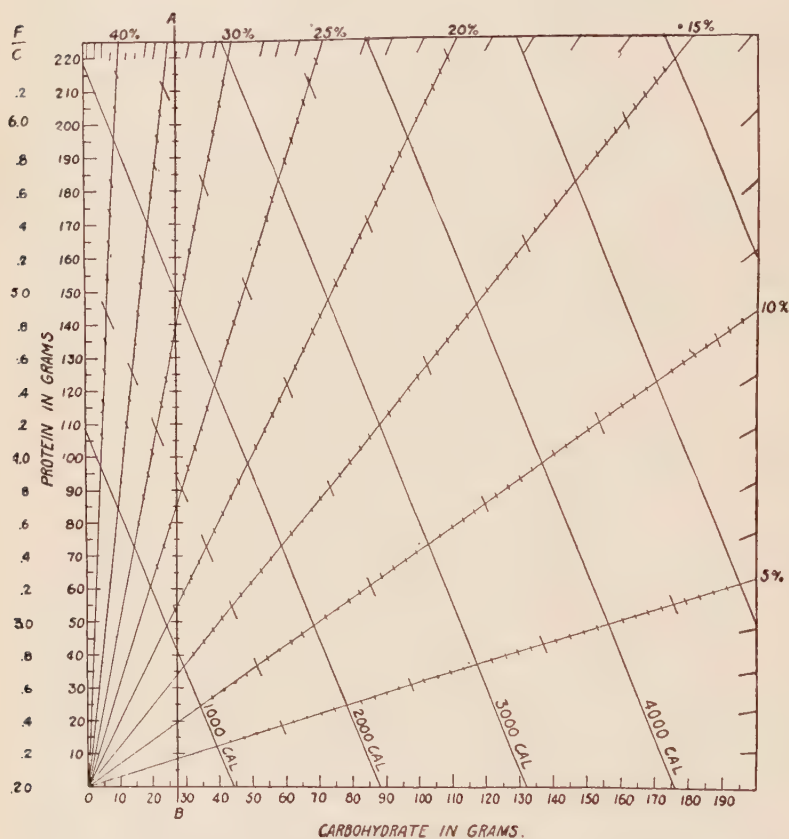


FIG. 53.—To calculate a diet formula, select the diagonal line representing the number of calories required; choose the radial line corresponding to the percentage of the total calories to be furnished by protein; from the intersection of these two lines read off the amounts of protein and carbohydrates on the axes; the intersection of the AB with the radial percentage line determines the factor $\frac{F}{C}$. This factor multiplied by the number of grams of carbohydrate equals the grams of fat required. (Hannon and McCann.)

strive to keep the protein metabolism as low as possible. The authors do not state what they do if this diet causes glycosuria. Presumably they either reduce the total calories

required by a period of undernutrition or else increase the carbohydrate metabolized by means of insulin.

Wilder,¹ on the basis of his experimental work with Winter, has adopted Shaffer's later ketogenic-antiketogenic ratio of 1 molecule of glucose to 2 of keto acids ($\frac{FA}{G} = 3$), but in his diets strives to give it a fairly wide berth. He endeavors to reduce the total metabolism, not by complete starvation, which he believes unnecessary, but by a diet planned to provide calories 20 per cent below the calculated maintenance requirement of an individual comparable in age, sex, height and weight. This he calls a "low maintenance diet." He restricts the daily protein intake to two-thirds of a gram for each kilo of body weight except in the case of children who may require more. He also restricts the carbohydrate as much as possible on the theoretical grounds that sugar strains a diseased or weakened carbohydrate-burning mechanism. Wilder balances the total available glucose and total available fatty acids by means of calculations based on a molecular ketogenic-antiketogenic ratio between 1.6:1 and 1.7:1. The calculations are rapidly made by means of the nomographic chart of Boothby and Sandiford,² which gives the basal food requirement, and a chart of Wilder's,³ which gives the division of calories among carbohydrate, fat and protein.

There is not much difference between these various modifications of Woodyatt's method. To my mind, McCann's modification seems the safest, but with a low carbohydrate tolerance one would be forced to adopt Wilder's dietary or else use insulin.

Insulin has of course given us much greater latitudes in our diets. We can now increase the carbohydrate tolerance by appropriate doses of this extract until it is sufficient to carry a diet of enough calories to keep the patient comfortable. This does not relieve us of responsibility in adjusting diets, and we should not use insulin for patients who do not need it or use it in doses that are larger than necessary. In every case the physician should balance the discomforts of insulin injections with the discomforts of a restricted diet.

For the details regarding the use of insulin the reader is

¹ Wilder: *Jour. Am. Med. Assn.*, 1922, 78, 1878.

² Boothby and Sandiford: *Boston Med. and Surg. Jour.*, 1921, 185, 337.

³ Wilder: *Jour. Am. Med. Assn.*, 1922, 78, 1878.

referred to the article by Banting, Campbell and Fletcher¹ and to the long discussion in Joslin's² book.

When a patient is found to be approaching or actually is in coma, we are still at a loss as to the best diet. His metab-

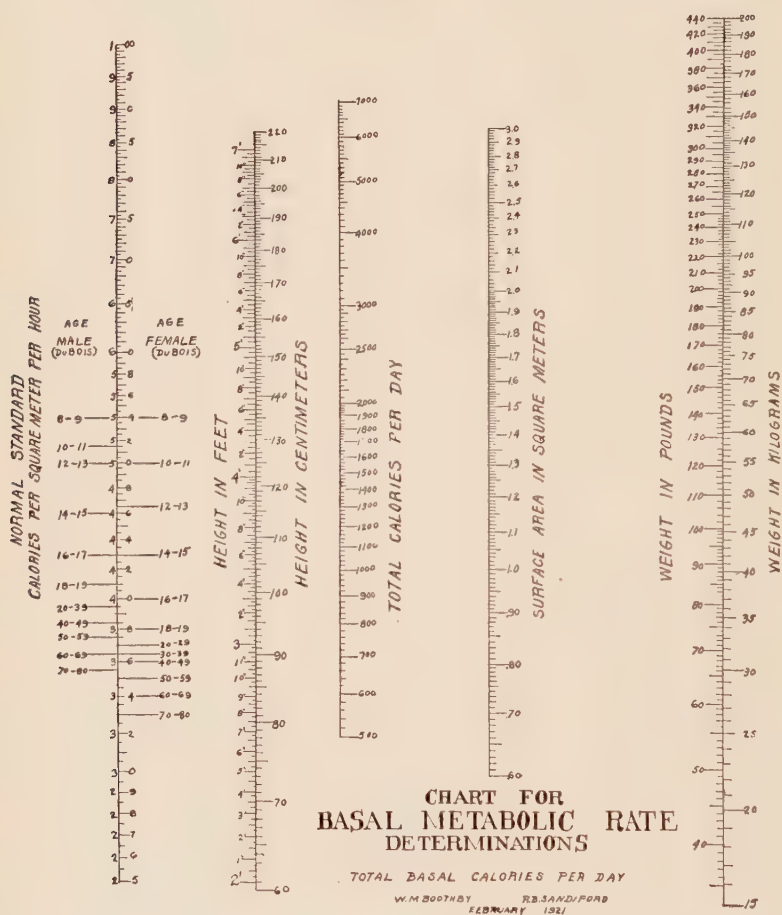


FIG. 54.—Boothby and Sandiford's chart for quick and accurate calculation of normal basal food calory requirement. The weight is located on the weight scale and the height on the height scale with pins (needles set in wooden handles). A straight edge connecting these two points crosses the surface area scale at the patient's surface area. The normal standard is located on the left-hand scale. The line connecting this point with the surface area crosses the calory scale at the basal twenty-four-hour calory requirement.

¹ Banting, Campbell and Fletcher: Jour. Metab. Res., 1922, 2, 547.

² Joslin: The Treatment of Diabetes Mellitus, third edition, Philadelphia and New York, Lea & Febiger, 1923.

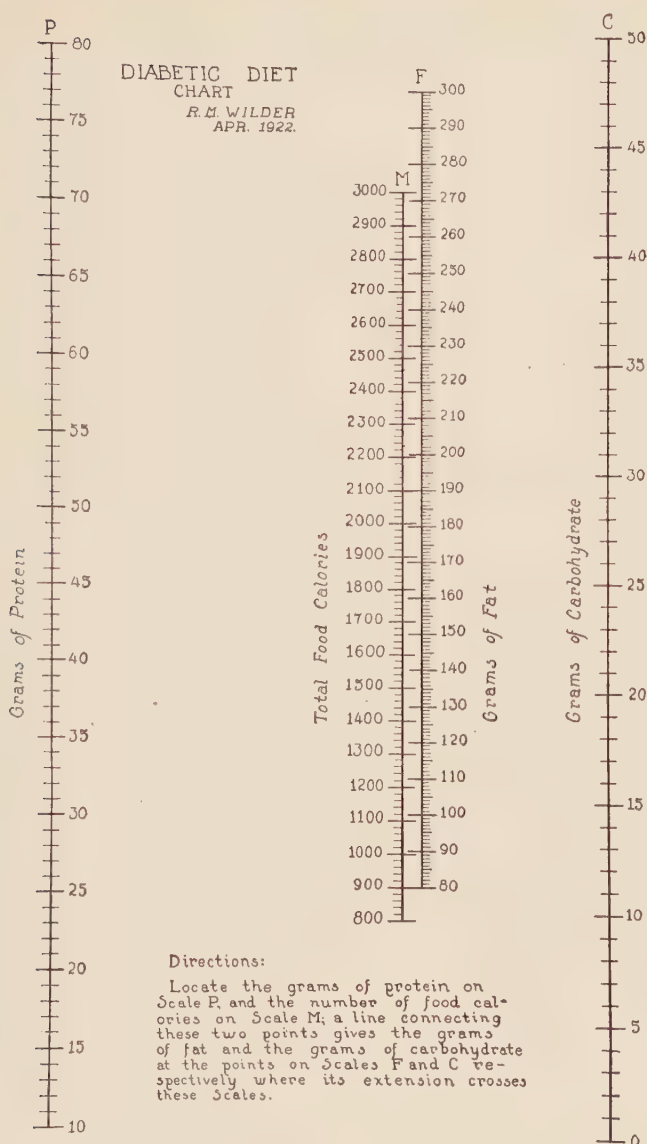


FIG. 55.—Diabetic diet chart. The grams of protein are located on Scale P, and the number of food calories on Scale M; a line connecting these two points gives the grams of fat and the grams of carbohydrate at the points on Scales F and C, respectively, where its extension crosses these scales. (Wilder.)

olism is racing along with its bit in its teeth. Body protein and fat are being oxidized, carbohydrate oxidation has almost disappeared. Whether or not we can increase this by giving carbohydrate is questionable. Fasting may reduce the total metabolism, but this is a relatively slow process. At the present time the only justifiable treatment is to give insulin in large doses combined, with carbohydrate to provide material for oxidation. There is still much evidence to support the use of bicarbonate of soda.

CHAPTER XIII. DISEASES OF THE THYROID.

CLASSIFICATION.

BEFORE making a detailed analysis of the work on the basal metabolism in thyroid disease, it is of advantage to survey briefly the whole question. There is still a certain amount of confusion in regard to nomenclature, and some of the minor clinical groups are classified differently by various writers. For a discussion of the etiology and pathology in thyroid disease, the reader is referred to the papers of Marine and his associates.¹ He has shown that in the various types of thyroid disease the process is initiated by a diminution in the iodine content of the gland. When this falls below a certain level there is stimulation with hypertrophy and hyperplasia of the epithelial cells, increase in the blood supply, and decrease in the colloid. This process often shows involution with complete recovery but it may lead to the formation of a large goiter. In some instances the process goes on to a physiological exhaustion of the cells and a stage of atrophy results. Glands which have reached one of the above-mentioned stages may again be stimulated thus complicating the picture.

Adenomas of the thyroid probably arise from cell rests, which on account of some stimulus react with growth. This seldom occurs except in goitrous glands. The differentiation of adenomas from other enlargements of the thyroid is not absolutely clear-cut, and there is a fairly gradual transition from the diffuse, uniform hyperplasia of simple goiter to the definitely encapsulated masses of typical adenomas. The type of cells in the mass depends upon the degree of differentiation of the original tissue at the time of the stimulus, and we may find adenomas of the fetal type of cells. Adenomas may pass through the stages of hypertrophy, hyperplasia, involution, or resting colloid stage. As a rule they are multiple, developing about the age of puberty.

Malignant tumors of the thyroid are fortunately rare.

¹ Marine and Lenhart: *Arch. Int. Med.*, 1911, 8, 265; 1911, 7, 506. Marine: *Endocrinology and Metabolism*, New York, D. Appleton & Co., 1922, 1, 269. Marine and Kimball: *Jour. Am. Med. Assn.*, 1921, 77, 1068.

Many types occur, carcinoma simplex being the most common. Thyroiditis, a generalized inflammation of the gland, is not often found in the clinic. The severe manifestations due to septic infection or tuberculosis are rare. Mild degrees of inflammation are perhaps much more common than we suspect, since they give few signs.

There have been many classifications of thyroid disease. Perhaps the one most commonly accepted is that which follows:

1. Colloid goiter.
2. Adenomas.
3. Exophthalmic goiter.
4. Myxedema.
5. Cretinism.
 - (a) Sporadic.
 - (b) Endemic.
6. Thyroiditis.
7. Malignant disease.

Diffuse Colloid Goiter.—In certain inland portions of the world such as the Great Lakes basin and certain cantons of Switzerland, many of the inhabitants show colloid goiters. These are diffuse symmetrical enlargements of the thyroid gland usually starting at the age of puberty. As a rule the function of the gland is normal and the enlargement alone causes the symptoms. This malady was well known to the ancients and its relationship to the water supply recognized at an early date. Marine¹ and his co-workers have shown that the disease is caused by a lack of iodine in the water and food, and that it can be prevented by giving small doses of iodine to girls at the age of puberty and to women during pregnancy.

The basal metabolism is almost always within or slightly below normal limits. Plummer² says that in the majority of cases in this country the basal metabolism ranges from 8 to 18 per cent below the normal average and that he has never seen one below the 18 per cent level. He also says that in a large series of myxedema patients and others with metabolism more than 20 per cent below the average, no patient has had a history of a diffuse colloid goiter. Apparently this type of gland rarely goes over to Graves' disease.

¹ Marine and Kimball: Jour. Am. Med. Assn., 1921, 77, 1068.

² Plummer: Oxford Med., rewritten, 1923, 3, 852.

Adenomas of the Thyroid.—Adenomatous enlargements of the thyroid in the majority of cases cause no constitutional symptoms, but in some cases are associated with hyperthyroidism. Such nodular masses are more apt to be found in glands which have previously been noticeably enlarged. They are usually multiple, giving a nodular feel to the mass, but sometimes they are first discovered on sectioning a portion of the gland removed at operation. Adenomas are benign, even those of fetal type, and, if removed at operation, there is no tendency toward recurrence.

Adenomas with Hyperthyroidism (Toxic Adenomas).—Plummer¹ has called attention to a group of hyperfunctioning adenomatous goiters and the subject is well discussed by Boothby and Sandiford.² The patients who have previously shown some enlargement of the thyroid gland begin to develop constitutional symptoms about the age of thirty-five or forty years. Sometimes the administration of iodine seems to initiate the increased function which continues even after the drug has been withdrawn. In the majority of cases the stimulus to increase activity is unknown. The symptoms develop gradually and the basal metabolism reaches an average of about 30 per cent above the normal. Exophthalmos does not often occur in this group. Removal of the adenomas cures the disease and causes the prompt fall of the basal metabolism to normal. Some of the patients improve on the administration of thyroxin. Iodine should be avoided.

Exophthalmic Goiter.—From the metabolic standpoint the most important thyroid disease is exophthalmic goiter, sometimes called hyperthyroidism, or Graves', or Basedow's disease. The best definition is that of Boothby:³

"A constitutional disease apparently due to an excessive, probably an abnormal, secretion of an enlarged thyroid gland showing pathologically diffuse, parenchymatous hypertrophy and hyperplasia. It is characterized by an increased basal metabolic rate with the resulting secondary manifestations, with a peculiar nervous syndrome and, usually, exophthalmos, with a tendency to gastro-intestinal crises of vomiting and diarrhea. The cause of the altered pathology and activity of the thyroid gland is not known."

¹ Plummer: Oxford Med., rewritten, 1923, 3, 857. Boothby: Oxford Med., 1923, p. 900.

² Boothby and Sandiford: *Physiol., Rev.*, 1924, 4, 69 (see pp. 108 and 110).

³ Boothby: Oxford Med., rewritten, 1923, 3, 913.

This seems to be a disease of civilization, occurring most frequently in cities. In its milder manifestations it is often confused with several other diseases and for this reason we seek every aid in diagnosis. Since the basal metabolism is increased roughly in proportion to the degree of hyperthyroidism, clinicians have used this as an aid in diagnosis and the matter will be discussed fully in the succeeding section. There is a tendency toward spontaneous recovery and perhaps the majority of cases will show marked improvement with ability to return to their usual manner of life, if treated with rest alone. Roentgen-ray or radium treatment seems to hasten recovery in about two-thirds of the cases. The administration of iodine in the form of Lugol's solution will usually cause a prompt but temporary remission of symptoms. Operative removal of about three-quarters of the gland still remains the standard method of treatment. Following the diminution of the mass of thyroid substance there is usually an improvement in the constitutional symptoms and marked fall in metabolism. In most cases the exophthalmos and grave cardiac damage cannot be relieved by treatment.

Myxedema.—Whenever the thyroid gland of an adult is diminished in amount by atrophy or operative removal to such an extent that the secretion (thyroxin) is seriously diminished, a constitutional disease known as myxedema results. This is characterized by diminished basal metabolism, myxedematous tissues and typical facies. Extreme cases with total absence of thyroid secretion show basal metabolic rates about 40 per cent below the normal. Such cases are quite rare but the milder manifestations seem to be encountered rather frequently. Both mild and severe forms usually improve promptly under the administration of thyroid extract or thyroxin. In this treatment basal metabolism determinations are of considerable service in controlling doses and we should make an effort to maintain the metabolism at about the normal level.

Cretinism.—Cretinism is a disease which originates during fetal life or infancy as a result of more or less complete lack of thyroid secretion. Physical and mental development are stunted and the general appearance is striking and characteristic. The endemic form is found not infrequently in the well-known goiter districts, a lack of iodine in the mother's organism being the probable cause of the failure in thyroid development. The sporadic form of the disease may

occur anywhere. It is probably due to the same uncertain factors which cause the myxedema of adults, but originating during infancy or childhood, causes a dwarfing of mind and body.

In all forms of cretinism, as in adult myxedema, the basal metabolism is low, but the comparison with normal standards often presents great difficulties. Thyroid extract or the purer thyroxin, in many cases, relieves all the symptoms causing a marvellous improvement with the return of the basal metabolism to normal. In other cases, particularly those of long standing, the results are extremely disappointing.

Malignant Disease of the Thyroid.—Malignant growths do not occur very often in the thyroid and when they do occur the correct diagnosis is seldom made until it is too late. As a rule they develop between the ages of forty and sixty in glands which have previously been goiterous or adenomatous. Usually the metabolism is above the normal but this does not serve to differentiate malignancy from other thyroid enlargements. Operation is advisable unless the disease has progressed to such an extent that complete removal is impossible. In such cases we must resort to the roentgen-ray or radium treatment.

THE BASAL METABOLISM IN THYROID DISTURBANCES.

Review of Literature.—We have reviewed in the preceding pages the main facts regarding the basal metabolism in diseases of the thyroid gland. Next we shall proceed to a more critical study of the original data. A complete review of the literature would be wearisome and confusing to the general reader. Those who are especially interested may consult the standard works with their extensive bibliographies.¹

¹ Grafe: *Ergeb. d. Physiol.*, 1923, **21**, Part II, 1. Biedl: *Innere Sekretion*, fourth edition, Berlin and Vienna, Urban & Schwarzenberg, 1922. Moebius: *Die Basedowische Krankheit*, Nothnagel's Handbuch 22, second edition, Vienna, 1906. Magnus-Levy: *Der Stoffwechsel bei Erkrankungen einiger Drüsen ohne Ausführungsgang*, von Noorden's Handbuch der Pathologie des Stoffwechsels, second edition, II, Berlin, A. Hirschwald, 1907, p. 325. Chovstek: *Morbus Basedowi und die Hyperthyreosen*, *Enzyklopädie der Klin. Medizin*, Berlin, Springer, 1917. McCarrison: *The Thyroid Gland in Health and Disease*, London, 1917. Boothby, Plummer and Wilson: *Diseases of the Parathyroid and Thyroid Glands*, Oxford Med., rewritten, 1923, **3**, 831; *Endocrinology and Metabolism*, New York, D. Appleton & Co., 1922. McCann, W. S.: *Calorimetry in Medicine*, Williams & Wilkins Company, Baltimore, 1924. (Also in *Medicine*, 1924, **3**, 1). Boothby and Sandiford: *Physiol. Rev.*, 1924, **4**, 69. Møller, Eggert, *Kliniske Undersøgelser over Basalstofskiftet ved Sygdomme i Skjoldbruskkirtlen*, Levin and Munksgaards Forlag, Copenhagen, 1925 (In Danish, has 213 references).

Early Studies in Metabolism Diseases in Germany.—Friedrich Müller¹ in 1893 compared the emaciation and loss of weight of exophthalmic goiter patients with their high caloric intake and came to the conclusion that the metabolism was increased. This was definitely proved shortly afterward by Magnus-Levy,² who demonstrated not only the increased oxygen consumption of hyperthyroidism, but also the low metabolism of cretinism and myxedema and the striking effect of thyroid extract in relieving the symptoms and raising the heat production. Indeed, he had by 1897 stated clearly almost all the important facts about metabolism in disease, and the contributions of later years have made comparatively few changes or additions.

Magnus-Levy used the Zuntz-Geppert apparatus, which gives satisfactory results in the hands of such a master of technic. Others,³ who worked with this same apparatus or with the Pettenkofer-Voit chamber, added to the data regarding the basal metabolism and studied the effects of thyroid extract and other preparations.

Metabolism Studies in America.—The possibilities of a more extensive clinical application of the method were realized in this country in 1912, and the Russell Sage Institute of Pathology,⁴ of New York City, planned the construction of an Atwater-Rosa-Benedict respiration calorimeter in a room adjoining a metabolism ward in Bellevue Hospital, with this as one of the main problems of a five-year campaign. After a few preliminary observations it became evident that the most important thing was a normal standard for comparison,

¹ Müller: *Deutsch. Arch. klin. Med.*, 1893, **51**, 335.

² Magnus-Levy: *Berl. klin. Wchnschr.*, 1895, **32**, 650; *Deutsch. med. Wchnschr.*, 1896, **22**, 491; *Ztschrh. klin. Med.*, 1897, **33**, 269.

³ Stüve: *Fest. Städt. Krankenhaus, Frankfurt, Mahlau*, 1896. Thiele and Nehring: *Ztschr. klin. Med.*, 1896, **30**, 41. Andersson and Bergman: *Skand. Arch. Physiol.*, 1898, **8**, 326. Hirschlaff: *Ztschr. klin. Med.*, 1899, **36**, 200. Jaquet and Svenson: *Ztschr. klin. Med.*, 1900, **41**, 375. Saloman: *Berl. klin. Wchnschr.*, 1904, **41**, 635. Steyrer: *Ztschr. exper. Pathol. u. Therapy.*, 1907, **4**, 720. Pribram and Porges: *Wien. klin. Wchnschr.*, 1908, **21**, 1584. von Bergmann: *Ztschr. exper. Pathol. u. Therap.*, 1909, **5**, 646. Undeutsch: *Inaug. Dissertation, Leipzig*, 1913.

⁴ Lusk: *Clin. Cal.* **1**, *Arch. Int. Med.*, 1915, **15**, 793. Riche and Soderstrom: *Clin. Cal.* **2**, *Arch. Int. Med.*, 1915, **15**, 805. Gephart and Du Bois: *Clin. Cal.* **3**, *Arch. Int. Med.*, 1915, **15**, 829. Du Bois: *Clin. Cal.* **14**, *Arch. Int. Med.*, 1916, **17**, 915. Gephart and Du Bois: *Clin. Cal.* **4**, *Arch. Int. Med.*, 1915, **15**, 835; *Clin. Cal.* **13**, *Arch. Int. Med.*, 1916, **17**, 902. Du Bois and Du Bois: *Clin. Cal.* **5**, *Arch. Int. Med.*, 1915, **15**, 868. Sawyer, Stone and Du Bois: *Clin. Cal.* **9**, *Arch. Int. Med.*, 1916, **17**, 855. Du Bois and Du Bois: *Clin. Cal.* **10**, *Arch. Int. Med.*, 1916, **17**, 863.

similar to the normal standards of temperature, blood-pressure, hemoglobin, etc. As a result, a considerable amount of time was spent in an analysis of the results on normal men and in the development of a new method of determining surface area. Soon it became clear that normal individuals showed basal metabolism within 15 per cent of the average, almost all of them coming within 10 per cent of the average. This made it fairly easy to tell whether or not a patient's metabolism was abnormally high or abnormally low. Meanwhile, Benedict,¹ of the Carnegie Nutrition Laboratory, was improving his small respiration apparatus and simplifying the technic until it became available for any well-equipped clinic. He was also making important contributions to the study of the normal metabolism. In his laboratory and that of Boothby the Tissot technic was improved and was shown to be practicable for clinical use. As a result of these advances we have now at our disposal a large number of determinations of the basal metabolism in thyroid diseases.

In the first publications from the Russell Sage Institute of Pathology² there is a summary of the early work of the Germans and the cases first studied by the author in this country. With our present knowledge, we suspect that the clinical diagnosis in some of the cases with low metabolism was faulty.

The conclusions of the Sage investigators were that the methods of direct and indirect calorimetry in exophthalmic goiter corresponded closely to each other; that the vaporization of water from the skin and lungs was greater than normal, but was proportional to the increase in heat elimination, since the goiter patients lost 25.7 per cent of their calories through vaporization, while the normal controls under similar conditions showed an average loss of 23.9 per cent. They found no abnormal increase in the specific dynamic action of protein and glucose and they confirmed the statement of Magnus-Levy that very severe cases of exophthalmic goiter show an increase of metabolism of 75 per cent or more above the normal average, severe cases 50 per cent or more, and mild cases less than 50 per cent, while a few mild and several atypical cases

¹ Benedict, F. G., and Tompkins, E. H.: *Boston Med. and Surg. Jour.*, 1916, **174**, 857, 898, 939. Benedict, F. G.: *Boston Med. and Surg. Jour.*, 1918, **178**, 667. Benedict, F. G. and Collins, W. E.: *Boston Med. and Surg. Jour.*, 1920, **183**, 449. Harris, J. A., and Benedict, F. G.: *A Biometric Study of Basal Metabolism in Man*, Carnegie Institution of Washington Publication No. 279, 1919.

² Du Bois: *Jour. Am. Med. Assn.*, 1914, **63**, 827; *Clin. Cal.* **14**, *Arch. Int. Med.*, 1916, **17**, 915.

and cases that had been operated upon might be within the normal limits. They recognized the increased basal metabolism as the cause of many of the symptoms and they demonstrated the reduction in metabolism caused by rest in bed.

Studies of Means and Aub in Boston.—The first extensive studies in which a large number of patients were followed for a considerable period of time were published by Means and Aub.¹ The last report is the most valuable for our purposes because it gives the results obtained in 2049 determinations on 1000 patients with various diseases. Means and his associates used the Benedict Universal apparatus and later the Benedict Portable, employing the Sage normal standards. The patients were divided as follows:

TABLE 63.—PERCENTAGES OF MEAN'S PATIENTS WITH SUBNORMAL AND SUPERNORMAL METABOLISM.

	Number of patients.	Subnormal, per cent.	Supernormal, per cent.
Clinically thyrotoxic	300	0.0	99.7 ²
Clinical myxedema and cretinism	32	100.0 ³	0.0
Goiters, clinically non-toxic	102	5.9	12.7
Borderline cases in which hyperthyroidism was suspected	290	4.1	36.2
Borderline cases in which hypothyroidism was suspected	70	21.4	12.9
Other endocrine diseases	41	48.8	24.4
Blood diseases (anemia, leukemia and polycythemia)	66	3.0	68.1
Miscellaneous non-endocrine diseases . .	99	8.1	20.2
Total, all groups	1000	9.3	30.2

OCCURRENCE OF SUBNORMAL METABOLISM.

Basal metabolic rate, per cent (inclusive.)	Group: Number of cases.							Per cent.
	Suspected hyperthyroidism.	Non-toxic goiter.	Miscellaneous non-endocrine.	Suspected hypothyroidism.	Other endocrines.	Blood diseases.	Total (all groups).	
-11 to -12	5	3	5	8	3	1	25	40.0
-13 to -14	3	2	2	3	3	0	13	20.5
-15 to -16	2	1	1	2	7	0	13	20.5
-17 to -18	1	0	0	0	3	0	4	6.5
-19 to -20	0	0	0	0	1	0	1	1.5
-21 or less	1	0	0	2	3	1	7	11.0

¹ Means: Boston Med. and Surg. Jour., 1916, 174, 864. Means and Aub. Jour. Am. Med. Assn., 1917, 69, 33; Arch. Int. Med., 1919, 24, 404; Arch. Int. Med., 1919, 24, 645. Means and Burgess: Arch. Int. Med., 1922, 30, 507.

² The one exception had very mild symptoms.

³ 26 cases which had received no thyroid.

OCCURRENCE OF SUPERNORMAL METABOLISM.

Basal metabolic rate, per cent (inclusive).	Group: Number of cases.							Per cent.
	Non-toxic goiter.	Suspected hypothyroidism.	Miscellaneous non-endocrine.	Other endocrines.	Suspected hyperthyroidism.	Blood diseases.	Total (all groups).	
+61 to +90	0	0	0	0	0	2	2	1
+41 to +60	0	0	0	0	6	10	16	8
+26 to +40	0	1	2	1	17	9	30	15
+19 to +25	0	3	5	3	22	10	43	21
+15 to +18	1	2	5	1	27	8	44	22
+11 to +14	12	3	8	5	33	6	67	33

Means' conclusions are as follows:

1. Patients with an outspoken clinical picture of hyperthyroidism invariably show increased metabolism, and those with definite clinical pictures of hypothyroidism invariably show decreased metabolism. Those with goiters, but no signs or symptoms of abnormal thyroid function, for the most part show normal metabolism.

2. Patients with atypical or incomplete clinical evidence of abnormal thyroid function may show normal or abnormal metabolism. The majority show normal metabolism.

3. By inference from the indirect evidence we believe that in these borderline thyroid cases, provided that in the first place a true basal rate is secured, and, provided that certain well recognized causes for increased metabolism, such as fever, acromegaly, leukemia and severe anemia are excluded, the finding of an increased basal metabolic rate is strong presumptive evidence of hyperthyroidism. In a similar way, provided that such conditions as starvation, hypopituitarism, and hypoadrenalism are excluded, a low metabolic rate is strong presumptive evidence of hypothyroidism.

4. To that extent, then, the metabolism test is distinctly useful in differential diagnosis. Like all other laboratory tests it should only be interpreted with due regard to all other clinical and laboratory findings, and with due regard for its limitations and pitfalls.

The Studies of Boothby in Rochester.—Boothby and Sandiford,¹ working at the Mayo Clinic, have had an extraordinary opportunity to study the metabolism in thyroid diseases and have used it to the utmost advantage. They have a large corps of well-trained assistants, and their clinical material is abundant and perhaps more thoroughly studied than that found anywhere else in the world. Without considering in detail their earlier publications, we can focus our attention

¹ Boothby: Jour. Am. Med. Assn., 1921, 76, 84; Endocrinology, 1921, 5, 1. Boothby and Sandiford: Laboratory Manual, Philadelphia and London, W. B. Saunders Company, 1920. Sandiford: Endocrinology, 1920, 4, 71. Boothby and Sandiford: Jour. Biol. Chem., 1922, 54, 783. Boothby: Oxford Med., revised 1923. Boothby and Sandiford: Physiol. Rev., 1924, 4, 69.

on their later summaries which deal with the basal metabolism data based on determinations made on about 12,000 subjects. They have used the open circuit spirometer technic and the Sage standards of normals. Approximately one-third of the patients were studied on one morning only.

TABLE 64.—COMPARISON OF THE BASAL METABOLIC RATE IN 6197 PATIENTS WITH THYROID DISORDERS STUDIED BEFORE 1922. (BOOTHBY.)

Diagnosis.	Cases.	Percentage range.								
		Above + 20.	+ 20 to + 16.	+ 20 to + 11.	+ 15 to + 11.	Normal + 10 to - 10.	- 11 to - 15.	- 11 to - 20.	- 16 to - 20.	Below - 20.
		%	%	%	%	%	%	%	%	%
Exophthalmic goiter	2569	93	..	5	..	2				
Recurrent exophthalmic goiter . .	320	90	6	..	2	2				
Adenoma with hyperthyroidism . .	1425	68	..	32						
Recurrent adenoma with hyperthyroidism	46	57	17	..	26					
Adenoma without hyperthyroidism	1111	100				
Recurrent adenoma without hyperthyroidism	62	90	8	..	2	
Colloid goiter	328	..	3	..	10	79	6	..	1	1
Myxedema	102	20	..	80
Postoperative myxedema	41	46	..	54
Questionable hypothyroidism . .	86	9	..	61	..	30
Cretinism	28	21	..	32	..	47
Thyroiditis	34	32	..	12	..	35	..	12	..	9
Malignant thyroid	45	22	..	9	..	67	2
Total	6197									

Their tables show the consistently high metabolism in exophthalmic goiter. They note that, with few exceptions, patients with this diagnosis having basal metabolism rates below 20 per cent came under their observation during a period of remission. In the adenoma cases the decision as to the presence or absence of hypothyroidism was based on the metabolism determination, therefore the group of adenoma cases without hyperthyroidism is entirely below the +10 per cent mark. The patients with colloid goiter, some of whom had colloid adenoma, showed a metabolism essentially normal. The myxedema patients were consistently low. Most of the cretins had previously received thyroid medication,

TABLE 65.—THE BASAL METABOLIC RATE IN CONDITIONS NOT DUE TO THYROID DISORDERS STUDIED BEFORE 1922. (BOOTHBY.)

Diagnosis.	Cases.	Percentage range.							
		Below -20.	-20 to -16.	-15 to -11.	-10 to +10.	+11 to +15.	+16 to +20.	Above +20.	-15 to +15.
		%	%	%	%	%	%	%	%
Normals	127	3.2	92.1	4.0	0.7	..	99.3
Migraine	31	6.4	93.6	100.0
Chronic nervous exhaus- tion	267	..	1.2	2.3	87.3	8.6	0.7	..	98.2
Neurasthenia	384	..	0.3	3.6	84.3	9.4	1.4	1.0	97.3
Obesity	94	1.1	3.2	6.4	80.7	7.5	1.1	..	94.6
Asthenia	36	..	2.7	11.2	77.8	8.3	97.3
Essential hypertension	170	0.6	73.0	15.8	7.2	3.4	89.4
Cardiac neurosis	99	..	1.0	2.0	83.9	10.1	1.0	2.0	96.0
Heart-block	10	80.0	10.0	..	10.0	90.0
Endocarditis	56	1.8	80.4	5.4	1.8	10.6	87.6
Myocarditis	55	1.8	..	3.6	81.9	10.9	..	1.8	96.4
Pericarditis	4	100.0	100.0
Congenital heart	5	80.0	20.0	100.0
Renal	127	4.0	1.6	3.2	72.4	12.6	4.0	2.4	88.2
Hodgkin's disease	1	100.0	..
Mental	34	3.0	3.0	8.9	61.7	17.6	2.9	2.9	88.2
Epilepsy	22	9.1	4.6	9.1	77.3	86.4
Gastro-intestinal	98	1.0	1.0	3.1	85.7	4.1	5.1	..	92.9
Gynecological	96	1.0	2.1	6.3	81.3	4.1	5.2	..	91.7
Malignancy	0	..	5.0	..	55.0	10.0	10.0	20.0	65.0
Dermatological	43	2.3	..	14.0	79.1	4.6	97.7
Pregnancy	30	70.0	10.0	10.0	10.0	80.0
Encephalitis	10	10.0	70.0	20.0	80.0
Dysphagia	65	16.9	6.2	10.7	63.1	3.1	76.9
Acromegaly	30	3.3	..	3.3	43.4	13.3	10.0	26.7	60.0
Hypopituitarism	58	12.1	25.9	15.5	34.5	5.2	3.4	3.4	55.2
Paget's disease	6	66.7	16.7	..	16.6	83.4
Addison's disease	13	15.4	..	7.7	69.2	7.7	76.9
Polycythemia	2	50.0	50.0	50.0
Secondary anemia	30	..	3.3	..	80.0	13.4	..	3.3	93.4
Anemia, splenic and pernicious	19	15.9	63.0	10.5	..	10.6	89.4
Leukemia, lymphatic and myelogenous	16	6.3	6.3	..	87.5	12.6
Questionable ductless glands	24	8.3	8.3	16.6	58.4	8.4	75.0
Sclerosis of central nervous system; tabes	20	90.0	10.0	100.0
Diabetes	68	17.7	10.3	7.3	52.9	..	5.9	5.9	60.2
Arthritis	69	2.8	2.8	5.7	75.3	11.6	1.4	..	92.6
Misc., not thyroid	178	..	2.7	5.6	77.1	8.4	4.0	2.2	91.1
Total	2417	2.1	2.2	4.6	77.1	8.3	2.6	3.1	90.0

TABLE 66.—THE BASAL METABOLIC RATE IN 1689 PATIENTS WITH THYROID DISORDERS STUDIED DURING 1922. *(BOOTHBY AND SANDIFORD.)

Diagnosis.	Cases.	Percentage range.									
		Above +75	+74 to +50	+49 to +21	+20 to +16	+15 to +11	+10 to -10	-11 to -15	-16 to -20	Below -20	Above +20
Exophthalmic goiter	452	12	40	40	4	3	1	92
Recurrent exophthalmic goiter	56	11	16	61	3	2	5	2	88
Adenoma with hyperthyroidism	346	2	11	52	13	22	65
Recurrent adenoma with hyperthyroidism	11	18	9	36	..	37	63
Adenoma without hyperthyroidism	544	100
Recurrent adenoma without hyperthyroidism	23	91	4	5
Colloid goiter	140	1	1	7	81	4	5	1	1
Myxedema	12	17	..	83	..
Postoperative myxedema	11	9	9	82	..
Questionable hypothyroidism	42	26	19	24	31	..
Cretinism	1	100
Thyroiditis	27	..	4	41	..	7	44	4	45
Malignant thyroid	24	..	8	4	4	13	58	..	13	..	12
Total number of cases	1689										

* "The 3331 cases summarized in tables 66 and 67 represent all patients on whom tests were made during 1922 with the exception of 13 in which a positive diagnosis of the presence of hyperthyroidism was not reached.

In a consideration of the significance of tables 66 and 67, the probability of errors in the determination of the basal metabolic rate must be evaluated. We estimate that in routine work in our laboratory there is a material error in about 1 per cent of the determinations and in an additional 5 per cent of the tests slight errors occur, the result of which is to place the patient either in the next higher or lower group, as arranged in the table. In about one-third of the patients with thyroid disorders only one determination was made and approximately one-half the patients who had other diseases, not involving the thyroid, had only one rate.

If in any group 100 typical cases with unquestioned diagnosis are selected and of whom sufficient basal metabolic rate determinations are made so that all errors are excluded, such a series will usually show a 99 per cent agreement with the characteristic metabolism for that condition.

With a few exceptions the patients with exophthalmic goiter having basal metabolic rates below +20 per cent came under our observation during a period of remission.

The patients listed under recurrent exophthalmic goiter and recurrent adenoma, with and without hyperthyroidism, include those who had had a previous partial thyroidectomy before any metabolism studies had been made in our laboratory and in whom the question of the necessity for further operative treatment was under consideration.

A basal metabolic rate of +10 per cent has been taken arbitrarily as dividing patients with adenomatous goiter into the groups with and without hyperthyroidism. While all cases with basal metabolic rates below +10 per cent are unquestionably not hyperthyroid, it cannot be assumed that all those with basal metabolic rates slightly above +10 per cent are necessarily hyperthyroid.

Only rarely does a cretin come under our observation who has not had thyroid medication; therefore the results presented in the table cannot be considered as the average of a group of untreated cases. Furthermore, the normal standards for children are not yet as accurately established as are those for adults." (Boothby and Sandiford.)

TABLE 67.—THE BASAL METABOLIC RATE IN CONDITIONS NOT DUE TO THYROID DISORDERS IN 1642 PATIENTS STUDIED DURING 1922. (BOOTHBY AND SANDIFORD.)

Diagnosis.	Cases.	Percentage range.							
		Below -20	-20 to -15	-15 to -11	-10 to +10	+11 to +15	+16 to +20	Above +20	-15 to +15
		%	%	%	%	%	%	%	%
Negative	76	6	84	9	1	..	99
Migraine	42	10	88	2	100
Chronic nervous exhaustion	191	1	1	5	86	6	1	..	97
Neurasthenia	210	..	1	11	80	6	..	2	97
Obesity	55	2	2	2	80	4	5	5	86
Asthenia	18	..	5	5	78	6	6	..	89
Essential hypertension	95	..	3	2	66	11	8	10	79
Cardiac neurosis	22	73	23	4	..	96
Cardiac miscellaneous	33	6	67	15	6	6	88
Endocarditis	48	..	2	2	65	21	4	6	88
Myocarditis	40	2	..	2	53	20	13	10	75
Pericarditis	5	80	20	80
Renal	80	2	2	14	69	4	1	8	87
Mental	28	..	4	4	82	7	..	3	93
Epilepsy	24	..	13	8	63	12	..	4	83
Gastro-intestinal	112	1	4	12	73	10	95
Gynecological	42	5	..	10	83	..	2	..	93
Malignancy	23	13	4	4	48	17	9	5	69
Dermatological	34	6	74	15	3	2	95
Pregnancy	29	79	10	7	4	89
Encephalitis	6	17	66	17	100
Dysphagia	14	57	14	..	29	29
Acromegaly	5	60	..	20	20	60
Hypopituitarism	14	7	15	14	50	..	7	7	64
Paget's disease	1	100	100
Addison's disease	12	17	67	8	8	..	92
Secondary anemia	25	96	..	4	..	96
Anemia, splenic and pernicious	36	3	..	3	53	8	19	14	64
Leukemia, lymphatic and myelogenous	15	27	7	6	60	34
Questionable ductless glands	1	100	100
Sclerosis of central nervous system; tabes	4	100	100
Diabetes	61	5	3	5	69	13	2	3	87
Arthritis	65	2	2	6	83	1	6	..	90
Miscellaneous, not thyroid	176	1	3	7	73	5	6	5	85
Total number of cases	1642	1	2	7	74	8	4	4	89

In this group there was also a certain amount of inaccuracy on account of the questionable normal standards for children and the uncertainty as to what sort of a child should be compared with a cretin.

In the table of patients not suffering from disease of the thyroid gland we notice that 90 per cent show metabolic

rates between +15 and -15 per cent and that three-quarters of these are within 10 per cent of the average. Plummer¹ gives a table (Table 68), showing the range of metabolism in unquestionable hypothyroidism.

TABLE 68.—UNQUESTIONABLE HYPOTHYROIDISM. (PLUMMER.)

	Basal metabolism, per cent.	Patients.
Myxedema, severe, idiopathic . . .	-25 to -42	51
Cretinism, congenital or infantile . . .	-22 to -35	18
Thyroiditis (no operation)	-12 to -32	3
Tuberculosis (no operation)	-22	1
Post-thyroidectomy, exophthalmic goiter	-15 to -35	17
Post-thyroidectomy, adenomatous goiter	-15 to -36	10
Post-thyroidectomy, thyroiditis	-22 to -38	3
Post-thyroidectomy, carcinoma	-16	1

The Work of Kessel, Hyman and Lande.—These workers² have published the details regarding a number of patients with exophthalmic goiter and conditions that resemble this disease. Since they have used a raised basal metabolism as the criterion for a diagnosis of true exophthalmic goiter, their results can only indirectly be applied to an analysis of the value of such determinations. We should be arguing in a circle if we used the metabolism to establish the diagnosis and then used the diagnosis to establish the value of metabolic determinations. They classify in one group 50 patients with frank exophthalmic goiter, all but 1 showing elevated basal metabolism, this exception being a young girl. Another group of 55 patients showed thyroid enlargement with no increase in basal metabolism and none of the nervous manifestations of exophthalmic goiter. Most of these patients had previously been falsely diagnosed as sufferers from hyperthyroidism. The last group, consisting of 86 patients, deserves special attention. Basal metabolism estimations made in only 30 of these cases were normal, and it seems probable that similar results would have been obtained in others of the group. They presented many of the symptoms of exophthalmic goiter, complaining of palpitation, dyspnea, headache, insomnia and loss of weight. They suffered from gastro-intestinal disturbances, vasomotor instability, tachy-

¹ Plummer: Oxford Med., rewritten, 1923, 3, 866.

² Kessel, Hyman and Lande: Arch. Int. Med., 1923, 31, 433. Hyman and Kessel: Jour. Am. Med. Assn., 1925, 85, 1017.

cardia, cardiac irregularities and tremor. Goiter was present in 72 of the 86 cases; asthenia and tremor were present in about one-quarter of the cases; most of them complained of nervousness; 12 had definite exophthalmia; and 19 von Grafe's sign. This is the symptom-complex that is ordinarily called "larval hyperthyroidism" or "forme fruste" or "Basedow's

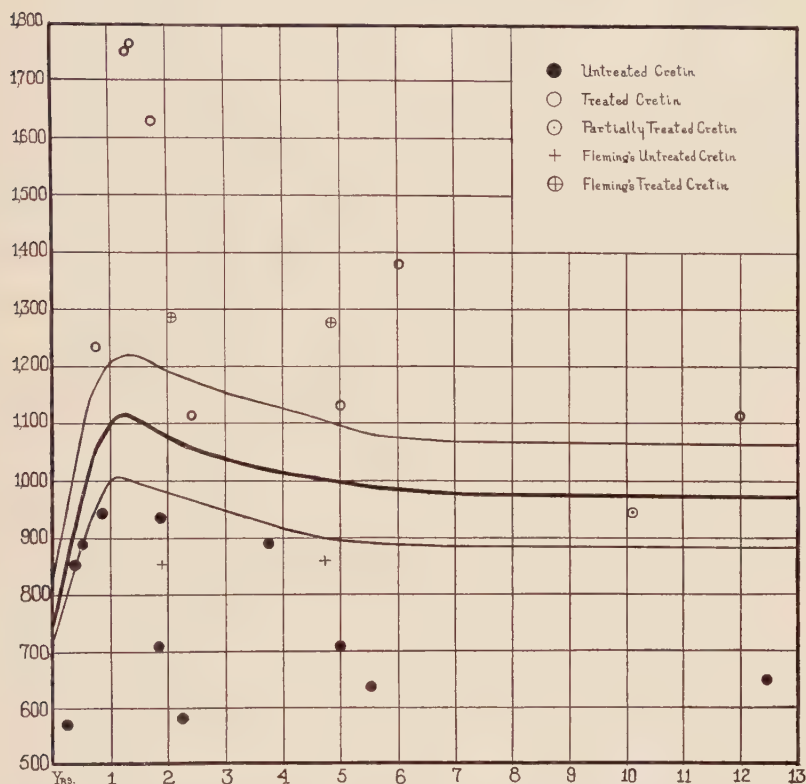


FIG. 56.—Basal metabolism of treated and untreated cretins; calories for each square meter with reference to age. (Talbot and Moriarty.)

disease." Kessel, Lieb and Hyman apply to this syndrome the term "autonomic imbalance" and believe that it is due to disturbances of the involuntary nervous system and that the thyroid enlargement is not causative. Everyone who has had much experience has seen patients that would fall into this group, but it is still questionable if we are safe in considering it a distinct disease which is not due to a disturbance of the thyroid gland.

Talbot's Studies in Cretinism.—Talbot and his associates¹ in Boston have investigated the metabolism of a number of cretins and have compared the data with their normal standards according to total calories, calories per kilogram of body weight and calories per square meter of body surface, as shown in Figs. 56 and 57. They noted that the depression

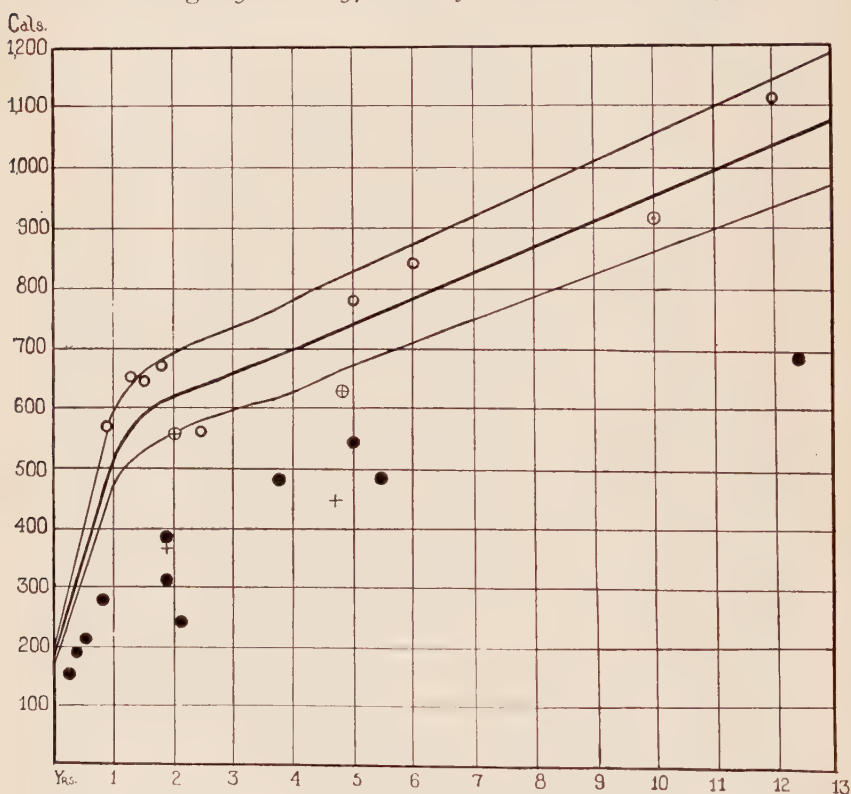


FIG. 57.—Basal metabolism of treated and untreated cretins, total calories with reference to age. The symbols are the same as in Fig. 56. (Talbot and Moriarty.)

in metabolism is much more striking if the total calories of the cretins are compared with the calories to be expected in normal children of the same age. This really superimposes the factors of retardation in growth and the depression of metabolism. A similar though less marked depression was found by Talbot² in some Mongolian idiots.

¹ Talbot and Moriarty: *Am. Jour. Dis. Child.*, 1923, **25**, 185.

² Talbot: *Monatschr. f. Kinderheilk.*, 1924, **27**, 465.

As a result of long experience with basal metabolism tests and a careful consideration of the various standards of reference Talbot has been able to make a diagnosis of cretinism in an infant three months old. Such an extraordinarily early diagnosis is of great importance and we may expect a new era in the therapy of cretinism if this becomes possible in many clinics.

Space does not permit us to review all the recent articles on the basal metabolism in thyroid disease. One of the most comprehensive, that of Møller,¹ is written in Danish. The author is rather conservative as to the value of the basal metabolism test, believing that some of the old classical symptoms of greater importance. Janet² in France has dealt chiefly with thyroid disturbances in childhood. Here in America Sturgis³ has written an excellent clinical review of myxedema pointing out the symptoms due to low metabolism. He emphasizes the need of care in the interpretation of metabolism tests and as an example mentions one apparently normal physician whose basal metabolism on three occasions was between -22 and -25 per cent. Barach and Draper⁴ have called attention to the interesting but little discussed group of patients with mild myxedema. Bowman and Grabfield⁵ have reported one myxedematous patient with metabolism 56 per cent below the average normal. This seems to be the lowest figure recorded in a human being.

A DISCUSSION OF RELIABILITY OF BASAL METABOLISM IN DIAGNOSIS.

There seems to be a general consensus of opinion that the level of the basal metabolism is the best guide to the activity of the thyroid gland. This has a sound physiological and clinical basis. We must remember, however, that we are dealing with a laboratory test and that it must not be accepted blindly. There are certain limitations which should be emphasized at this point. The technic is difficult, and errors of 10 or 20 per cent may be made, especially by beginners.

¹ Møller, E.: *Kliniske Undersøgelser over Basalstofskiftet ved Sygdomme i Skjoldbruskkirtlen*, Levin and Munksgaards Forlag, Copenhagen, 1925.

² Janet, H.: *Le Métabolisme basal en Clinique*, Jouve et Cie, Paris, 1922.

³ Sturgis: *Med. Clin. N. Am.*, 1922, **5**, 1251.

⁴ Barach and Draper: *Jour. Am. Med. Assn.*, 1925, **84**, 740.

⁵ Bowman and Grabfield: *Ibid.*, 1923, **81**, 209.

Even in the best hands there is a possible error of 2 or 3 per cent. In addition to this there are rather wide fluctuations in the daily metabolism of certain individuals. The first few tests with a thyroid patient may be 10 or 20 per cent too high. Some normal individuals consistently show rates 10 to 15 per cent or even more above or below the normal. The chances are that these various sources of error will partially neutralize each other, but if they all happen to fall in the same direction the result will be far off from the truth.

In every disease there is a tendency to variation from the typical which occurs in certain individuals and there are few hard and fast rules in diagnosis. It is very seldom that we should allow any single symptom or laboratory test to outweigh a mass of evidence. A slavish adherence to the basal metabolism test as an index of diagnosis may lead the physician to trouble, first because the test does not always give the true basal metabolism, and second because even the true basal metabolism is not always the indication of the correct diagnosis. God forbid that we make our diagnoses by machinery!

There are certain conditions in which the basal metabolism is frankly incorrect in making a clinical diagnosis. Patients with myxedema and cretinism who have been receiving thyroid extract may have normal basal metabolism, while they are retaining still most of the phenomena of the disease. Exophthalmic goiter patients in their remissions may still be considered as sufferers from a lesion of the thyroid. In other cases a tendency toward an abnormally low metabolism may be combatted by anemia or fever or some other factor which tends to raise metabolism. In emaciated patients with hyperthyroidism we do not know the influence of the inanition in depressing the heat production. In one such patient the writer cautiously tried a few days of starvation, which resulted in a marked drop in heat production.

In the literature that we have just quoted there are a number of patients in whom the basal metabolism did not correspond with the clinical diagnosis. Several cases that had been diagnosed as exophthalmic goiter by such excellent clinicians as Magnus-Levy, Falta, and others, did not have an increased metabolism. In the analysis by Means and Burgess we note that the untreated myxedema patients and cretins all showed a low metabolism, but that a considerable

number with suspected hypothyroidism failed to do so. In many of these cases the test was probably made as a routine measure without expectation of a positive result, since every clinician frequently suspects hypothyroidism when the mass of evidence points rather to another diagnosis. Conversely, we note that two-thirds of the patients with suspected hyperthyroidism fail to show an increased metabolism. The authors state that, while some of this group were really suffering from hyperthyroidism, the rest were cases of psychoneurosis, effort syndrome, organic heart disease in which, because of nervousness or tachycardia or some such sign, the clinician wished to exclude thyrotoxicosis.

The group reported by Kessel, Lieb and Hyman under the name of "autonomic imbalance" is puzzling. The majority of clinicians would probably call most of these exophthalmic goiter and yet such basal metabolism tests as were performed fell within the normal limits. These investigators found a large number of patients referred to them with a diagnosis of exophthalmic goiter who certainly did not have the disease. This common error in diagnosis has been noted by all who have made a special study of the thyroid. One of the most striking examples is the report of Peabody, Sturgis, Tompkins and Wearn.¹ They found in a group of soldiers with irritable heart (neuro-circulatory asthenia) almost all had been falsely diagnosed hyperthyroidism. No clinician with much autopsy experience pretends to be infallible.

Bearing in mind the limitations of the test and of the clinical diagnosis, few students regard the metabolism determination absolutely diagnostic. Crile² considers that the basal metabolism estimation provides a valuable but not specific test for the presence of hyperthyroidism. He believes that metabolism estimations are of value in the differential diagnosis of borderline cases but are of little value in the determination of the operability or prognosis of cases of hyperthyroidism. Christie,³ in Crile's Clinic, considers that there are two things more important than the basal metabolism in

¹ Peabody, Sturgis, Tompkins and Wearn: *Am. Jour. Med. Sci.*, 1921, 161, 508. Peabody, Wearn and Tompkins: *Med. Clin. North America*, 1918, 2, 507.

² Crile: *The Thyroid Gland*, second edition, Philadelphia and London, W. B. Saunders Company, 1923.

³ *Ibid.*, p. 141.

the diagnosis. The first is a positive anamnesis; the second is a dilatation of the heart with a rapid rate and no other cause. He speaks of the group of patients who have had mild exophthalmic symptoms for a long time with marked cardiac and eye signs and a metabolism only 15 to 25 per cent above the normal. In these the disability is due to the devastating effect of the chronic disease.

Else¹ has called attention to the fact that the curves for the metabolism rate and the clinical symptoms in any given case are not necessarily parallel except in mild cases. He believes that in severe cases the rise in the metabolism is proportionately greater than the other symptoms at the onset of the disease, that a fall in metabolism during the latter stages is more striking than the improvement in clinical signs. In cases having frequent exacerbations he finds that the rate may be normal, or below normal, in the interval, although the symptoms are present continually.

METABOLISM PHENOMENA OTHER THAN BASAL.

Carbohydrate and Protein Metabolism.—The chief effect of the thyroid secretion is to increase the total heat production, but there are also certain effects on the carbohydrate and protein metabolism. There is a good deal of conflicting evidence regarding the level of the blood sugar and the form of the blood-sugar curve in exophthalmic goiter. At one time, this was much used as an aid in the diagnosis of thyroid disease but it seems to be passing out of vogue. Many observers have noted abnormally high blood sugar in exophthalmic goiter patients after the ingestion of 100 grams of glucose and in some cases glycosuria also. Conversely, there is a tendency toward a low blood sugar in hypothyroidism with an increased glucose tolerance. Studies on these subjects have been published by Geyelin,² Hamman and Hirschman,³ Denis, Aub and Minot⁴ and Janney and Isaacson.⁵ Sanger and Hun⁶ have followed the respiratory quotient in 10 exophthalmic goiter patients after the ingestion of 1.75 grams of glucose per kilogram of body weight.

¹ Else: *Basal Metabolism*, Boston, Sanborn Company, 1922, p. 157.

² Geyelin: *Arch. Int. Med.*, 1915, **16**, 975.

³ Hamman and Hirschman: *Arch. Int. Med.*, 1917, **20**, 761.

⁴ Denis, Aub and Minot: *Arch. Int. Med.*, 1917, **20**, 964.

⁵ Janney and Isaacson: *Arch. Int. Med.*, 1918, **22**, 160.

⁶ Sanger and Hun: *Arch. Int. Med.*, 1922, **30**, 397.

Their fasting respiratory quotients averaged 0.76 and fasting blood sugar 0.99, whereas the 10 normal controls show an average respiratory quotient of 0.80 and blood sugar of 0.85. The goiter patients showed an abnormally high blood-sugar curve for two hours after the ingestion of glucose and the respiratory quotient rose in most cases to a point between 0.90 and 1, going distinctly higher than the normal controls. The high respiratory quotients obtained in exophthalmic goiter after glucose ingestion shows that in most cases there is no diminution in the inability to oxidize carbohydrate or convert it into fat. The glycosuria would seem to be due to a rise of blood sugar above the renal threshold. Sanger and Hun believe that the sharp rise in blood sugar and in respiratory quotient indicate a diminished ability of exophthalmic goiter patients to store glycogen in the liver. This would be in accord with the work of Cramer¹ on rats. While there is some evidence in favor of this hypothesis, we must remember that the respiratory quotients of 0.76 to 0.80 usually found in hyperthyroidism fourteen hours or more after the last meal, indicate that there is still a considerable amount of carbohydrate stored in the body. Similar quotients are found on fasting fever patients who have been receiving liberal diets up to fourteen hours before their morning test. We might expect about the same level of quotient in a normal man, who by means of continual light exercise, maintained his total metabolism at a level which corresponded to that of the goiter patients.

Storage of Carbohydrate in Hyperthyroidism.—Much light is thrown on the question of glycogen storage by a calorimeter experiment which has not previously been published. A young man, Franklin K., with a metabolism about 40 per cent above the normal received in his diet 2500 to 3400 calories a day up to February 11, 1916. On the morning of the 12th he received only 106 calories, 8 grams of carbohydrate and 18 grams of protein. After this insignificant meal he was fasted until the afternoon of February 14. His heat production, which had been 78.4 calories per hour, fell to 77.6; his respiratory quotient which had been 0.805 on February 11 dropped to 0.75 on the third day of fasting, indicating that on this day he was deriving about 8 per cent of his calories from carbohydrate. His nitrogen balance was slightly nega-

¹ Cramer and Krause: *Proc. Royal Soc., B*, 1913, 86, 550.

tive when receiving 3000 calories and this probably represents his total heat production. Allowing for a gradual fall in heat production and percentage of calories derived from carbohydrate, we can estimate that he must have had about 300 to 360 grams of carbohydrate stored in his liver at the beginning of the fast. This is about the amount we would expect in a normal man. It is interesting to note that Benedict's¹ fasting subject, Levanzin, showed almost exactly the same respiratory quotient on the second and third days of fasting as this patient with exophthalmic goiter.

Protein Metabolism.—It was the high level of nitrogen excretion and difficulty in obtaining nitrogen balance that led Friedrich Müller to the assumption of a high total metabolism in exophthalmic goiter. It is quite possible, though it has not yet been proved, that in certain extreme cases there is an actual toxic destruction of protein such as we find in fever. By toxic destruction we mean that the protein breakdown cannot be controlled by the liberal administration of carbohydrate and fat, but remains far above the normal level. In such a case, nitrogen balance cannot be attained on an intake of 8 to 12 grams of nitrogen per day, and a nitrogen minimum of 3 or 4 grams can never be approached on a low-protein diet. In exophthalmic goiter, all the experiments are complicated by the necessity for giving enough food to cover the increased basal metabolism and also a surplus of 75 to 100 per cent in order to meet the demands of the almost incessantly active patient. The problem might be solved if the patient could be kept in a respiratory cabinet for several days on a very liberal diet low in protein.

Boothby and Sandiford,² have carefully reviewed this subject adding many long metabolism experiments of their own. They found it necessary to give a large excess of calories above the basal in order to attain nitrogen balance, and they accounted for part of this excess by showing that in hyperthyroidism a given amount of work requires about twice the expenditure of calories that it does in normal individuals as shown in Table 69. They found a striking improvement in the muscular efficiency of one exophthalmic goiter patient

¹ Benedict, F. G.: Carnegie Institution of Washington Publication No. 203, 1915.

² Boothby and Sandiford: *Med. Clin. North America*, 1921, 5, 425; *Jour. Am. Med. Assn.*, 1923, 81, 795; *Phys. Rev.*, 1924, 4, 69.

TABLE 69.—COST OF WORK EXPRESSED AS NET GRAM CALORIES FOR EACH HORIZONTAL KILOGRAM METER.*

Diagnosis.	Subjects.	Average basal metabolic rate.	Net gram calories for each horizontal kilogrammeter.	Deviation from normal of 1.20.
Normal	5	-10	1.20	
Diabetes mellitus	4	-13	1.09	-10
Myelogenous leukemia	2	+20	1.10	-8
Anorexia nervosa	1	-22	1.12	-7
Lymphatic leukemia	1	+65	1.19	-1
Addison's disease	1	-8	1.27	+6
Chronic nervous exhaustion	1	+5	1.34	+12
Myxedema	5	-28	1.36	+13
Hypertension	3	+4	1.43	+19
Carcinoma of the thyroid	1	+43	2.31	+93
Exophthalmic goiter	12	+52	2.24	+87
Adenoma with hyperthyroidism	1	+47	2.86	+138

* Calculated as follows:

$$\frac{(\text{T.C.H.W.} - \text{T.C.H.B.}) \times 1000}{\text{M.H.} \times \text{Wt.}} = \text{Net gram calories for each horizontal kilogrammeter}$$

where T.C.H.W. = total calories per hour at work, T.C.H.B. = total calories per hour in bed, M.H. = meters per hour, Wt. = walking weight of subject in kilograms and the constant 1000 to convert large calories into gram calories.

The basal heat production in bed under standard conditions was chosen for the base-line because the interest lay in the net cost of all work, including that for maintaining the upright position. (Boothby and Sandiford.)

following thyroidectomy. They did not study the nitrogen minimum and the work is not absolutely conclusive, but they are justified in saying that their evidence indicates that "there is no measurable increase in the endogenous protein metabolism in exophthalmic goiter: therefore, it cannot be the cause of the increased basal metabolism in this disease."

Rudinger,¹ tried to find the nitrogen minimum in Basedow's disease, studying 2 young patients. The diets used contained 2500 to 3500 calories and 2 to 3.1 grams of nitrogen. In 1 patient, the urine nitrogen fell gradually until he was excreting 3.19 to 5.7 grams of nitrogen a day, figures above the normal. In the other patient, with more severe manifestations of the disease, the nitrogen did not go below 6.5 grams. These results are not conclusive. Lauter and Jenke² in one patient with hyperthyroidism obtained a nitrogen minimum excretion of 1.47 grams per day, a figure slightly lower than their normal controls.

¹ Rudinger: *Wien. klin. Wchnschr.*, 1908, 21, 1581.² Lauter and Jenke: *Deutsch. Arch. f. klin. Med.*, 1925, 146, 323.

Epstein and Lande¹ have found that blood cholesterol is low in hyperthyroidism and high in myxedema. The cause of this is not clear.

Specific Dynamic Action of Food.—The action of various foods in causing a rise in the metabolism in hyperthyroidism has been studied by Magnus-Levy,² Pribram and Porges³ and Undeutsch.⁴ Magnus-Levy found no departure from the normal, the others believed that the specific dynamic action was somewhat increased. Aub and Means, found that the specific dynamic action of glucose was normal in Graves⁵ disease and Sanger and Hun,⁶ reached the same conclusion. The Sage,⁷ investigators studied a few patients in the calorimeter and found no clear departure from the results obtained in controls. We must conclude that no abnormality in the dynamic action of foods has yet been demonstrated, but the number of experiments is small and the technic difficult.

Direct and Indirect Calorimetry.—There is no evidence pointing toward any profound qualitative change in the metabolism of protein, fat and carbohydrate. Any such change if profound or extensive would cause a disagreement between the methods of direct calorimetry and indirect calorimetry as calculated by the usual method. The Sage investigators,⁸ noted a fairly close agreement between the two in the patients with hyperthyroidism studied in their respiration calorimeter. The total for the direct method was 2.9 per cent lower than the other and the individual short experiments showed an average divergence of 4.1 per cent. This tendency of the direct calorimetry to run 2 or 3 per cent lower than the indirect calculations has been encountered in several other diseases and is probably due to the loss of a few calories stored in the patient's body or bed-clothing.

Water Metabolism.—In the Sage calorimeter,⁹ it was found that patients with severe and moderately severe hyper-

¹ Epstein and Lande: *Arch. Int. Med.*, 1922, **30**, 563.

² Magnus-Levy: *Berl. klin. Wchnschr.*, 1895, No. 30; *Ztschr. f. klin. Med.*, 1897, **33**, 269.

³ Pribram and Porges: *Wien. klin. Wchnschr.*, 1908, **21**, p. 1584.

⁴ Undeutsch: *Exper. Gaswechseluntersuchungen bei Morbus Basedowi*, Inaug. Dissert., Leipzig, 1913.

⁵ Aub and Means: *Arch. Int. Med.*, 1921, **28**, 173.

⁶ Sanger and Hun: *Arch. Int. Med.*, 1922, **30**, 397.

⁷ Du Bois: *Clin. Cal.* **14**, *Arch. Int. Med.*, 1916, **17**, 915.

⁸ Du Bois: *Clin. Cal.* **14**, *Arch. Int. Med.*, 1916, **17**, 915.

⁹ Soderstrom and Du Bois: *Clin. Cal.* **25**, *Arch. Int. Med.*, 1917, **19**, 931.

thyroidism in a chamber at 23° C. lost about 40 grams of water per hour through skin and lungs. Some large patients with severe symptoms lost more than this amount but the ventilation of the calorimeter was not sufficient to make an accurate measurement possible. In practically all the cases where a satisfactory measurement could be made, it was found that the patients with Graves' disease eliminated about the same percentage of calories through skin and lungs as did the normal controls. In other words, we can say that the water of vaporization is increased in proportion to the total heat elimination.

Reaction to Drugs.—It has been known for some time that men and animals with hyperthyroidism are sensitive to epinephrin. Goetsch,¹ has used this as a clinical test, finding an increase in pulse-rate, blood-pressure and certain other symptoms in a large proportion of patients with hyperthyroidism. Unfortunately, similar positive reactions have been found in a number of other conditions. Peabody, Clough, Sturgis, Wearn and Tompkins,^{2, 3, 4} obtained positive reactions in neuro-circulatory asthenia (effort syndrome), in many psychoneurotics, convalescents from various acute infectious diseases and in 14 per cent of apparently normal young men. Larsen, Paddock and Alexander,⁵ found it in asthma. At the present time the consensus of opinion seems to be that the Goetsch test is not strictly diagnostic of hyperthyroidism. It remains important, however, as a physiological fact and a warning that we should be particularly careful in giving small doses of epinephrin if ever they are needed by exophthalmic goiter patients. The response to the usual doses may be extremely alarming.

There is an abnormal sensitiveness to atropine in a much higher proportion of exophthalmic goiter patients than in normal controls.⁶ Reid Hunt,⁷ in a long series of studies, has shown that an increased amount of thyroid secretion in

¹ Goetsch: *Endocrinology and Metabolism*, New York and London, D. Appleton & Co., 1922, 1, 475; *New York State Jour. Med.*, 1918, 18, 259.

² Peabody, Clough, Sturgis, Wearn and Tompkins: *Jour. Am. Med. Assn.*, 1918, 71, 1912.

³ Wearn and Sturgis: *Arch. Int. Med.*, 1919, 24, 247.

⁴ Peabody, Sturgis, Tompkins and Wearn: *Am. Jour. Med. Sci.*, 1921, 161, 508.

⁵ Larsen, Paddock and Alexander: *Jour. Immunol.*, 1922, 7, 81.

⁶ Kessell and Hyman: *Am. Jour. Med. Sci.*, 1923, 165, 513.

⁷ Hunt: *Am. Jour. Physiol.*, 1923, 63, 257.

certain animals causes an increased resistance to the poison acetonitril (methyl-cyanide) whereas in other animals it causes a lower resistance. This has been used as a test of thyroid preparations and in a few human cases as a diagnostic measure.

The Relationship of Pulse to Basal Metabolism.—It has long been known that the pulse-rate is roughly proportional to the level of the metabolism. This has been discussed often in the literature. Murlin and Greer,¹ found that the pulse-rate multiplied by the pulse-pressure was a better indicator of the level of the metabolism than the rate alone. The relationship of pulse-rate to the gaseous exchange of normal individuals is well shown in the monograph of Harris and Benedict.² The curve of the normal pulse-rate under basal conditions as drawn by Sutliff and Holt³ has already been shown on page 192. Helmreich⁴ has compared the pulse-rate and caloric production of children under various conditions. He has observed in normal boys eight to fifteen years of age that the pulse-rate obtained first with the subject lying down increases 28 per cent in the sitting position and 40 per cent in the standing position, while the oxygen consumption increases only 8 and 10 per cent with these changes. Similar results were obtained when a boy was strapped on a table which could be tilted at various angles. Helmreich concludes that there are two kinds of pulse accelerators. The first as represented by muscular work is "dynamic" and has a causal relationship to increased metabolism. The second variety is "static" and goes with the diminution of heart output per beat. Blood accumulates in the lower part of the body and the heart is filled less during each diastole.

Pulse-rate in Hyperthyroidism.—The writer,⁵ in 1916, speaking of the simpler objective tests in Graves' disease, made the following statement: "The rapidity of the heart is perhaps the best guide, but the heart is often affected by other conditions and damage to the heart may outlast the other symptoms." Means and Aub,⁶ have repeatedly called attention

¹ Murlin and Greer: *Am. Jour. Physiol.*, 1914, **33**, 253.

² Harris and Benedict: *Carnegie Institution of Washington Publication No.* 279, 1919.

³ Sutliff and Holt: *Arch. Int. Med.*, 1925, **35**, 224.

⁴ Helmreich: *Ztschr. f. d. ges. exp. Med.*, 1923, **36**, 226.

⁵ Du Bois: *Clin. Cal.* 14, *Arch. Int. Med.*, 1916, **17**, 915.

⁶ Means and Aub: *Arch. Int. Med.*, 1919, **24**, 645.

to the importance of the pulse-rate as a guide to the condition of the patient. They found a close parallelism between pulse-rate and basal metabolism in about 60 per cent of their cases

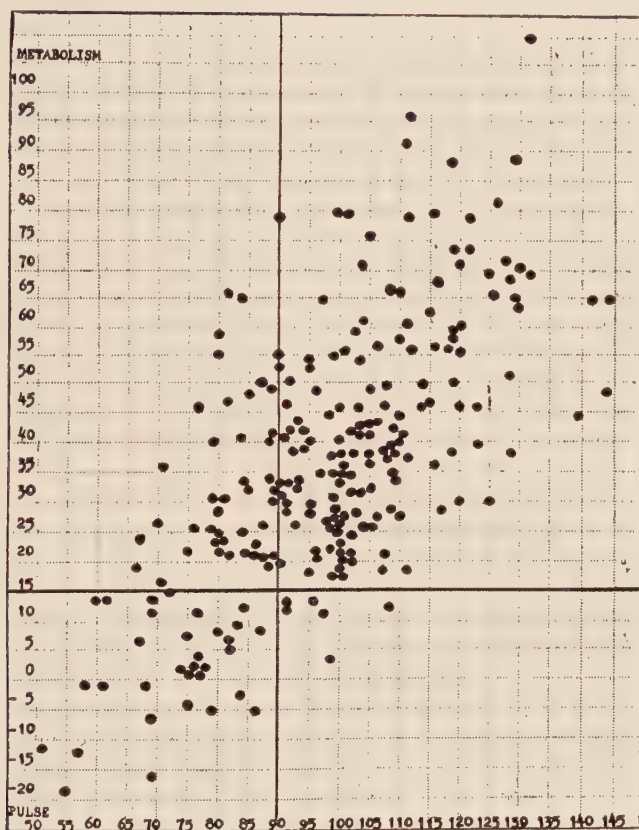


FIG. 58.—Two hundred and thirty-eight observations charted according to pulse-rate and basal metabolism. All of the dots in the upper right square indicate the observations with a metabolism greater than +15 per cent and pulse 90 per minute or greater; in the left upper square are those with metabolism greater than +15 per cent but pulse below 90; in the right lower square are those with a metabolism below 15 per cent but pulse greater than 90, and in the left lower square are those with a metabolism below +15 per cent and pulse below 90. It is apparent that a composite curve of all the dots would indicate the general tendency of the tachycardia to be more marked in patients with a high metabolism and of a less degree in those with a low metabolism. (Sturgis and Tompkins.)

and in the remainder a certain amount of parallelism. They believe that a study of the rate in a given individual is much more reliable as an indication of change than any compari-

son between different individuals. Sturgis and Tompkins¹ extended the number of comparisons and found a fairly constant relationship, as will be seen from Figs. 58 and 59 reproduced from their work. They state that an increased basal

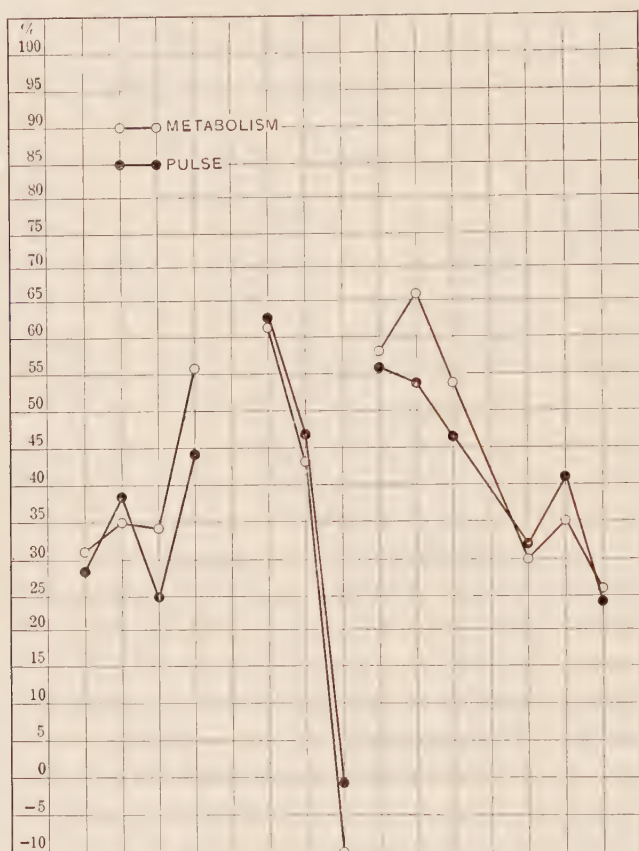


FIG. 59.—Illustration of the parallelism between the basal metabolism and pulse-rate in exophthalmic goiter. The pulse and metabolism have both been charted in per cent of normal, the normal pulse having been considered 70 per minute. (Sturgis and Tompkins.)

metabolism is seldom found with a pulse-rate at complete rest below 90 per minute and rarely found with the rate below 80. This is a matter of considerable practical importance.

Pulse-rate and Pulse-pressure.—Read² has studied the relationship of blood-pressure as well as pulse-rate in a

¹ Sturgis and Tompkins: Arch. Int. Med., 1920, 26, 467.

² Read: Arch. Int. Med., 1924, 34, 553.

series of 600 basal metabolism tests and his results are shown in Fig. 60. According to his calculations the formula $0.75 (\text{pulse-rate} + 0.74 \text{ pulse-pressure}) - 72 = \text{basal metabolic rate}$ he can find the basal metabolic rate within 10 per cent in half the cases. There is a tendency in the higher basal rates, beginning at about 55 per cent for the combined pulse-rate and pulse-pressure figures to increase out of all proportion to the metabolism. Read connects this with the diminution

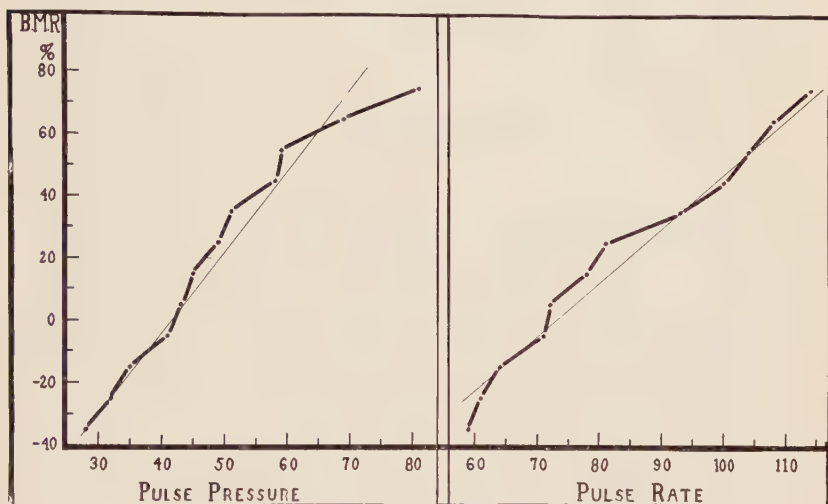


FIG. 60.—Read's analysis of 600 basal metabolism tests. The dots connected by the heavy line, represent the mean values for pulse-pressure and pulse-rate as they are affected by the basal metabolic rate. The light straight line is the line of regression for pulse-pressure and pulse-rate, respectively, on basal metabolic rate and is the best fitting straight line which can be drawn through the dots. It is the ideal "line of means."

in muscular efficiency noted by Plummer and Boothby in exophthalmic goiter.

Minot and Means¹ have recently made the important observation that the pulse-rate elevation in leukemia bears almost exactly the same relationship to increase in metabolism as it does in Graves' disease. This is probably more than a coincidence. Davies, Meakins and Sands² were able to show that the minute volume of the heart in hyperthyroidism was increased in proportion to the metabolism. Lindhard³

¹ Minot and Means: *Arch. Int. Med.*, 1924, **33**, 576.

² Davies, Meakins and Sands: *Heart*, 1924, **11**, 299.

³ Lindhard: *Pflüger's Arch.*, 1915, **161**, 233.

had demonstrated this in normal subjects. Schick, Cohen and Beck¹ noting the slow pulse found in children after certain infectious diseases were led to suspect a lowered basal metabolism. They confirmed their suspicions in a series of tests employing the Krogh apparatus.

In conclusion, we must emphasize the fact that the pulse-rate is a symptom of major importance and should be studied frequently when the patient is at complete rest. Only a rash clinician disregards its warnings.

THEORIES CONCERNING THE CAUSATION OF EXOPHTHALMIC GOITER.

Hyperthyroidism and Dysthyroidism.—The first theory was that exophthalmic goiter was due to an increase in the amount of thyroid secretion. Since that original and simple hypothesis various writers have ascribed certain symptoms to the additional involvement of other endocrine glands and of the involuntary nervous system. The hypothesis of a “dysthyroidism” rather than “hyperthyroidism” has gained a certain degree of popularity. According to this, the symptoms of exophthalmic goiter are due to a change in the nature of the thyroid secretion rather than to a mere increase in amount. Magnus-Levy² presents the arguments against this theory in a masterly fashion. Falta, Newburgh and Nobel³ believe in hyperfunction rather than in dysfunction and consider that the difference in symptoms is due to differences in the constitution of the patient.

We know that in an individual without thyroid secretion life is maintained for long periods with a metabolism about 40 per cent below the average level. Thyroxin or thyroid extract given to such an individual usually causes a complete restoration to health. Thyroid extract given to normal men causes an increase in metabolism and many of the symptoms of Graves' disease. Given to animals in large doses, it can produce increased metabolism, rapid heart beat, loss in weight and strength and gastro-intestinal symptoms. Exophthalmos

¹ Schick and Cohen: *Am. Jour. Dis. Child.*, 1925, 30, 291. Schick, Cohen and Beck: *Ibid.*, 1926, 31, 228.

² Magnus-Levy: *von Noorden's Handbuch*, Berlin, 1906, 1, 1.

³ Falta, Newburgh and Nobel: *Ztschr. f. klin. Med.*, 1921, 72, 97.

has not yet been reproduced in experimental animals with the exception of the cats in which Cannon¹ united the phrenic nerve to the vagus, thus producing a stimulation with each respiration. The causation of exophthalmos remains unexplained. Plummer considers that patients with toxic adenoma show a pure hyperthyroidism and that in exophthalmic goiter the secretion of the thyroid is not only increased but also somewhat imperfect, or that some of the series of reversible reactions into which it enters are not progressing normally. His brilliant success in relieving the symptoms by giving iodine has lent much support to his theory. Definite proof will come if someone succeeds in isolating a compound similar to thyroxin but differing in chemical structure and capable of reproducing the manifestations of Graves' disease.

So-called Mixed Cases.—Several writers have reported that they have observed the symptoms of myxedema and hyperthyroidism in the same patient. Even if a certain patient does have a mixture of symptoms, it does not mean that he has both diseases. In borderline cases of hypothyroidism the diagnosis is wrong about half the time. The same can be said of hyperthyroidism. We must remember that some of the symptoms of hyperthyroidism, such as exophthalmos, tremor and cardiac damage, may persist after the thyroid secretion itself has fallen to or below normal.

Kessel, Lieb and Hyman² believe that a disturbance of the involuntary nervous system plays an important rôle in the causation of exophthalmic goiter and regard the goiter as a purely secondary and symptomatic feature of Graves' disease.

There is much evidence to support the view of a close interrelationship between the various ductless glands. Such relationships exist between many organs of the body. Unfortunately, the factors which influence thyroid secretion do not lend themselves very well to study, since thyroid secretion cannot be measured directly and its indirect effects do not reach a maximum for several days. The thyroid, as Aub³ has pointed out, is probably a slow and rather steady regulator of metabolism.

¹ Cannon, Binger and Fitz: *Am. Jour. Physiol.*, 1915, **36**, 363.

² Kessel, Lieb and Hyman: *Arch. Int. Med.*, 1923, **31**, 433.

³ Aub: *Jour. Am. Med. Assn.*, 1922, **79**, 95.

A considerable amount of work has been done on the effect of the adrenals on metabolism. Gradinescu¹ removed the adrenals from 1 dog and 3 cats and found that there was a drop in metabolism. At the same time there was a marked drop in body temperature, which would in itself cause some diminution of heat production. The action of adrenalin, in causing a rise of the respiratory quotient due to an increased combustion of sugar, has been shown by several authors. The most conclusive work is that of Lusk and Riche,² who found a great increase in the carbohydrate oxidation in 2 dogs.

Adrenalin acts upon the metabolism in a few minutes. After a subcutaneous injection of 0.5 cc of a 1 to 1000 solution Irene Sandiford found an increase in metabolism of 10 to 20 per cent and an increase in pulse-rate.³ She points out the similarity of the hyperglycemia after adrenalin to the carbohydrate plethora associated with the specific dynamic action of glucose described by Lusk.⁴

Aub, Forman and Bright⁵ noted a fall of about 25 per cent in the metabolism of cats after adrenalectomy. In studying cats under urethane anesthesia they found that removal of the adrenals causes a prompt fall, even if the thyroid gland had previously been removed. They believe that the adrenal and thyroid mechanisms are separate and that the adrenal helps in acute chemical regulation and may be the basis of the increased rate seen during excitement. The more slowly acting regulation would then be accomplished normally by the thyroid secretion.

Marine and Baumann⁶ have found that if they remove just the right amount of suprarenal cortex in rabbits there is an increase in metabolism followed by a gradual fall. A previous thyroidectomy abolishes or lessens greatly the rise in metabolism caused by the injury to the adrenals. They believe that there is a relationship, or rather antagonism, between the adrenal cortex and the thyroid.

¹ Gradinescu: *Arch. f. d. ges. Physiol.*, 1913, **152**, 187.

² Lusk and Riche: *Arch. Int. Med.*, 1914, **13**, 673.

³ Sandiford: *Am. Jour. Physiol.*, 1920, **51**, 407. Boothby and Sandiford: *Ibid.*, 1923, **66**, 93.

⁴ Lusk: *Elements of the Science of Nutrition*, third edition, Philadelphia and London, W. B. Saunders Company, 1917, p. 297.

⁵ Aub, Forman and Bright: *Am. Jour. Physiol.*, 1922, **61**, 326.

⁶ Marine and Baumann: *Jour. Metab. Res.*, 1922, vol. **21**; *Am. Jour. Physiol.* 1922, **59**, 353; *Jour. Metab. Res.*, 1922, **1**, 777.

It has been suggested that the increased metabolism of exophthalmic goiter is due to the muscular twitchings and tremors. Magnus-Levy¹ made some experiments on the tremor of paralysis agitans and found that it caused only 5 to 20 per cent increase in metabolism. Aub, Forman, Bright and Uridil² made cats thyrotoxic by thyroxin and observed that the high metabolism persisted even under urethane anesthesia, with complete relaxation of the muscles and even after the adrenal glands were removed.

Aub³ has reviewed the effect of the various organs on metabolism. The gonads seem to have slight effect. Alterations of the basal metabolism are found in diseases of the pituitary gland, but perhaps only in such cases as also have thyroid involvement.

We shall take up these various endocrine glands in the next chapter.

In exophthalmic goiter the evidence indicates an overstimulation of the thyroid, an overproduction of thyroxin perhaps an alteration in its structure, a diminished storage of iodine-containing substances in the gland. We have little evidence regarding the rate of destruction and we do not know whether or not there is an increased sensitivity of the tissues to thyroxin. The disease affects the involuntary nervous system and other tissues besides the thyroid. The cause of exophthalmic goiter is unknown.

DISEASES OF THE THYROID: TREATMENT.

In Hypothyroidism.—Plummer and Boothby⁴ have shown that the results are clear-cut and almost quantitative when thyroxin is given intravenously. One milligram of the crystalline substance injected into a vein causes an average increase of 2.8 per cent in the basal metabolic rate and therefore one can predict that a 10 milligram dose will increase the metabolism from -40 per cent to -12 per cent. In a large series of cases the average variation from the figure of 2.8 was 0.7, the largest plus variation 2.8, the largest minus

¹ Magnus-Levy: *Ztschr. f. klin. Med.*, 1906, **60**, 177.

² Aub, Forman and Bright: *Am. Jour. Physiol.*, 1922, **61**, 326. Aub, Bright and Uridil: *Am. Jour. Physiol.*, 1922, **61**, 300.

³ Aub: *Jour. Am. Med. Assn.*, 1922, **79**, 95. Aub and Taylor: *Endocrinology*, 1922, **6**, 255.

⁴ Boothby: *Oxford Med.*, rewritten, 1923, **3**, 948.

variation 1.8. They have followed the curve of the basal metabolism of many patients with complete myxedema who have received thyroxin intravenously, and have established the rate at which the metabolism rises and falls. By these curves several important facts have been demonstrated. They have shown that 12 to 14 milligrams of active thyroxin must be present in the body to maintain the basal metabolic

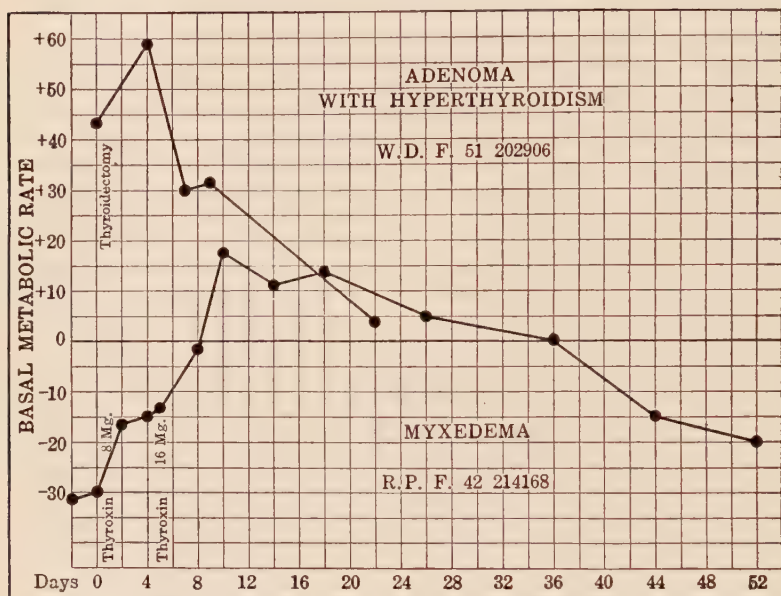


FIG. 61.—On the upper curve the basal metabolic rates of a patient having adenoma with hyperthyroidism are plotted, showing the original preoperative rate and the immediate postoperative rise in the metabolic rate, followed by the drop to normal after partial thyroidectomy. The lower curve illustrates the effect on the metabolic rate of a myxedematous patient of two intravenous injections of 8 and 16 milligrams of thyroxin, from which can be calculated the amount of thyroxin needed to bring such a patient to a normal basal metabolic rate, and therefore the presumable amount of thyroxin in the body, and also the rate at which the thyroxin is destroyed or eliminated. The daily dose was not started until after the fifty-second day, as it was desired to see the duration of the effect of the intravenous medication. (Boothby.)

rate at the normal level. After one large intravenous dose there is a latent period of about twelve hours, then begins a definite reaction with headache, nausea, and occasionally vomiting, pain in the back, legs, and joints, with increase in the pulse and temperature. On the second day the sub-

jective symptoms are most marked, being probably due to the sudden decrease in edema. Between the third and tenth day the curve in the basal metabolism reaches its apex. By this time there has been a marked change in the appearance and mental attitude of the subject. The descending portion of the curve is much more gradual than the rise, and by extrapolation it is known that thyroxin is lost or destroyed at the rate of 0.2 and 0.4 milligrams daily in a myxedematous patient. This "rate of decay" of thyroxin in the human subject has been shown by Boothby to follow a definite curve similar in shape to the fall in metabolism as the effects of adrenalin are wearing off though of course the time relationships are very different. The matter is discussed by Kendall¹ in his Chandler Lecture. There is reason to believe that the same rate of loss occurs in normal people and exophthalmic goiter patients but is counter-balanced by the secretion from the gland. The therapeutic indications are therefore clear. Once the basal metabolism of a patient with complete myxedema has been brought to the normal level it must be maintained by an appropriate daily dose of thyroxin in some form.

The intravenous administration is not essential. The same effects can be obtained by the oral administration of thyroxin or its salts, or by dessiccated thyroid or fresh thyroid tissue. Boothby and Plummer have found that in some patients the absorption from the gastro-intestinal tract is variable, being poor in certain cases, especially those with colloid goiter. The same variability in absorption holds true for desiccated thyroid preparations. There is also a great difference in the strength of the various commercial thyroid extracts. We must remember, therefore, that in giving doses by mouth it is desirable to standardize clinically or by means of basal metabolism determinations, not only the preparation but also the individual patient.

Thyroxin, the active principle of the thyroid gland was isolated in crystalline form by Kendall in 1915 and studied by him in a long series of investigations.² The clinical studies of Plummer, Boothby and others have shown that the pure

¹ Kendall: *Indust. and Eng. Chem.*, 1925, **17**, 525.

² Kendall: *Jour. Am. Med. Assn.*, 1915, **64**, 2042; *Collected Papers of the Mayo Clinic*, 1915, **7**, 393, 422; 1916, **8**, 513; 1919, **11**, 417, 424. *Indust. and Eng. Chem.*, 1925, **17**, 525.

thyroxin is just as potent as thyroid extract in relieving the symptoms of cretinism and myxedema. Thyroxin contains iodine, but not all of the iodine in the gland, and it is quite possible there are some other constituents that possess physiological activity, though for clinical purposes these are not important. Preparations much less pure than crystalline thyroxin have been isolated which contain the active principle of the gland. Baumann, who first discovered the iodine in the thyroid in 1895¹ isolated a substance from the gland

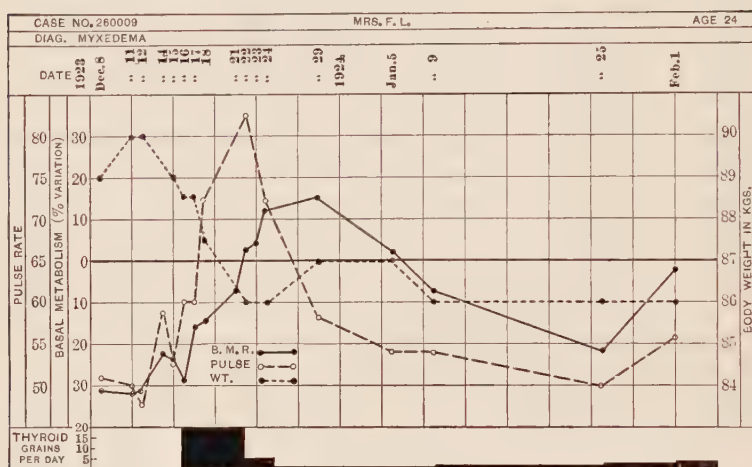


FIG. 62.—Effect of thyroid extract in severe myxedema. (Patient of Means.) The continued line shows the basal metabolic rate, the interrupted line the pulse-rate, and the dotted line the weight. The black blocks at the foot of the chart show the dosage of thyroid. The initial dose was 20 grains per day, the final dose 4 grains per day.

called thyroidine (iodothylin) containing about 10 per cent of iodine which was physiologically active. An iodine-containing substance iodo-thyro-globulin which is probably a globulin existing as such in the gland has also been isolated. It has a variable iodine content ranging from a trace to 1.7 per cent. Kendall's thyroxin contains 65 per cent of iodine and accounts for one-fourth of the total iodine content of the gland. Its molecular weight is 585 and the empirical formula $C_{11}H_{10}O_3NI_3$.

Dr. J. H. Means has kindly sent me a chart of one of his myxedema patients previously untreated. It will be noted

¹ Baumann: Ztschr. f. physiol. Chem., Strassburg, 1895, 21, 319; 1896, 22, 1.

that the dosage of thyroid extract was at first too high and then too low. After a few trials a proper dosage was secured. This chart shows beautifully the extreme sensitiveness of the metabolic rate to the amount of thyroid ingested.

On page 302 we spoke of Talbot's work¹ on the diagnosis of of cretinism. He has obtained the best therapeutic results by giving enough thyroid extract to bring the basal metabolism up to the level expected in a normal child of the same age.

Treatment of Hyperthyroidism.—Most cases of hyperthyroidism run a self-limited course and comparatively few are seen during the period of increasing severity. This has given some observers the impression that it does not make much difference what form of therapy is used. On the other hand there are many cases that progress to a point of alarming symptoms with great rapidity and others that drag along for years without visible improvement. Few scientific observers have had the courage to follow the basal metabolism of a large group of Basedow's patients over a course of several months without treatment. We have a fairly good control group in the cases observed by Kessell, Lieb and Hyman² treated chiefly by rest in bed. "Aside from iodine (syrup of ferrous iodide), given to reduce the neck circumference, no other drug was generally employed." The importance of this iodine medication was not realized at that time but the good results obtained were probably partly due to this drug as has been pointed out by Plummer and Boothby.³

Rest.—It has long been recognized that rest in bed causes a marked improvement in the symptoms of patients with exophthalmic goiter. There is a corresponding fall in the basal metabolism, which is by no means entirely due to falsely high readings on the first test when patients are unaccustomed to the procedure. The writer⁴ in 1916 found that rest in bed for a week or more caused a drop in metabolism of more than 10 per cent, and concluded that there was at that time no proof that any conservative form of medical treatment caused a greater fall in metabolism. When exophthalmic goiter patients first reach a hospital they are as a rule tired by the journey and excited by the new surroundings. We

¹ Talbot and Moriarty: *Am. Jour. Dis. Child.*, 1923, **25**, 185.

² Kessell, Lieb and Hyman: *Jour. Am. Med. Assn.*, 1922, **79**, 1213; *Arch. Int. Med.*, 1923, **31**, 433.

³ Plummer and Boothby: *Jour. Iowa, State Med. Soc.*, 1924, **14**, 66.

⁴ Du Bois: *Clin. Cal. 14, Arch. Int. Med.*, 1916, **17**, 915.

must therefore expect exacerbation of symptoms during the first few days, with a distinct improvement as they become accustomed to their surroundings. After the first rapid drop which has been noted by all observers the tendency toward a fall in the basal metabolism and improvement of the clinical symptoms is much less striking. The physician becomes discouraged and tries some method of treatment.

Hundreds of remedies have been tried in exophthalmic goiter and have had their enthusiastic advocates. Among those which have been almost discarded we find the serum of thyroidectomized horses, Beebe's thyrotoxic serum, ergotin and quinine hydrobromate, atropine, bromides, etc. There is no striking evidence that these have accelerated the tendency toward spontaneous recovery.

Roentgen-ray Therapy.—The roentgen-rays were discovered by Roentgen in 1895 and first used in thyroid disease five or six years later. Since that time many investigators have employed this method with more and more encouraging results as the technic has improved. A good résumé of the history of this method of treatment will be found in the paper of Means and Holmes.¹ The earlier reports are of interest but of much less importance for our purposes than the modern investigations in which the basal metabolism has been studied over a long period of years. The best recent work is that of Means and Holmes, who have brought up to 1923 the data on all their cases studied in the Massachusetts General Hospital since 1914 and described in earlier reports by Means and Aub.²

Their cases are first treated in the hospital ward, if possible, and then in the out-patient clinic. They use relatively short wave lengths, a long target skin distance, and three or more portals of entry, one on each side of the neck and one over the thymus region. Great care is taken to avoid reddening and tanning of the skin. The doses are repeated at intervals of about three weeks and are not continued beyond five months unless very definite benefit has been obtained. Their results are shown in Figs. 63 and 64.

¹ Means and Holmes: *Arch. Int. Med.*, 1923, **31**, 303.

² Means and Aub: *Jour. Am. Med. Assn.*, 1917, **69**, 33; *Arch. Int. Med.*, 1919, **24**, 645. Means: *Med. Clin. North America*, 1920, **3**, 1077. Holmes and Merrill: *Jour. Am. Med. Assn.*, 1919, **73**, 1693. Holmes: *Am. Jour. Roentgenol.*, 1921, **8**, 730.

The composite curve demonstrates clearly the fall in basal metabolism which occurred while most of the patients were taking only a partial rest cure in addition to their roentgen-ray treatment. It will be noted that the pulse-rate ran parallel to the basal metabolism and that the weight increased rapidly during the early portion of the treatment. One striking case (Fig. 64) is given in an individual chart. A barber with a severely toxic type of exophthalmic goiter was treated with roentgen-ray. His metabolism fell to normal, but two

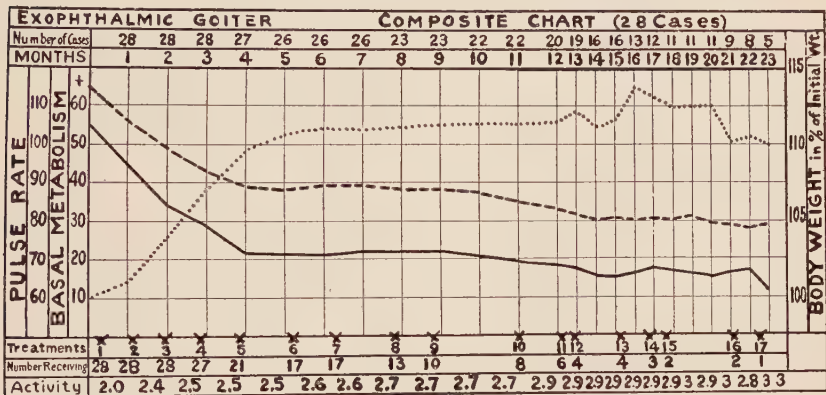


FIG. 63.—In this and the next chart the perpendicular rulings are at intervals of one month. The solid black line denotes basal metabolism (per cent variation from Sage Institute standards), the interrupted line represents the pulse-rate and the dotted line represents body weight. In Figs. 63 and 64 the weight is expressed in per cent of the initial weight which is taken as 100 per cent. Fig. 63 is composite. Roentgen-ray treatments are denoted by X. Activity in Fig. 63 is shown in the following manner: 1 denotes complete rest in bed; 2, partial rest; 3, following usual occupation. For the composites these figures for all individuals composing the composite are averaged. (Means and Holmes.)

years later he returned with a classical picture of myxedema which was relieved by thyroid extract.

The theory on which the use of the roentgen-rays is based depends on the fact that all active cells are highly sensitive to radiation. About one-fifth of the dose necessary to produce reddening of the skin will cause cessation of the menstrual flow and a similar dose to the testicles will cause a disappearance of spermatozoa from the seminal fluid. Small doses will stop the secretion from the parotid gland and from the mammary glands. Larger or repeated doses will cause atrophy. Some surgeons have stated that roentgen-ray treatment to

the thyroid makes subsequent operation more difficult; others have denied this.

Means and Holmes found that about two-thirds of their patients treated with roentgen-ray showed either improvement or recovery. The remaining one-third neither improved nor grew worse. If good results are not secured in a few months they advise operation. In certain cases in which operation is intended from the start, roentgen-ray may be of service in making the patient a better operative risk.

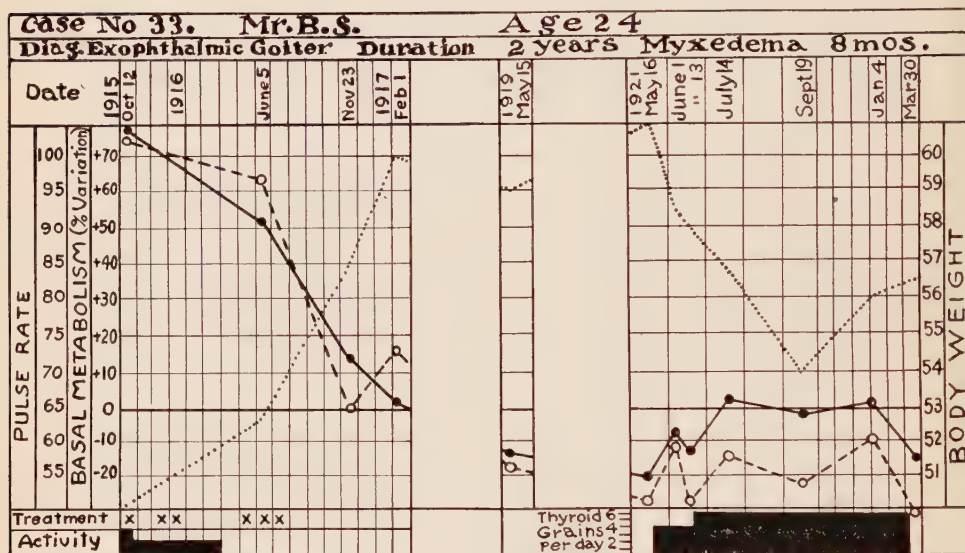


FIG. 64.—In the right-hand portion the dose of thyroid given during the period of myxedema is shown by width of shading. (Means and Holmes.)

Read¹ of San Francisco is even more enthusiastic about roentgen-ray therapy than the Boston investigators. In a series of 50 patients so treated he has had satisfactory results with no deaths and no patients made worse by irradiation.

Plummer, in a discussion of a paper by Means and Holmes,² stated that it was his impression that roentgen-ray treatments reduced to some degree the average intensity of the course of the disease, but he did not feel that the curves shown after treatment represented much more than the natural tendency

¹ Read: Calif. State Jour. Med., January, 1924, 22, 10.

² Means and Holmes: Trans. Assn. Med. Phys., 1922, 37, 198.

toward recovery. Crile¹ prefers to use surgery, since the mortality is low, time is saved, and the cure is made more certain.

Radium.—Loucks² has treated 180 cases with radium and has given an enthusiastic report. Within ten days of the treatment the exophthalmic goiter patients show improvement. About the third week there is a return of symptoms due to the radium reaction. After two months all the symptoms are usually better. Some cases are symptom-free after six months and others take two or three times as long. Few require a second radiation. Loucks studied the basal metabolic rate of his patients and found that in some cases, followed over two and a half years, the readings remained within the normal limits.

Treatment with Iodine.—Iodine has been used in the treatment of exophthalmic goiter by many clinicians but no one seems to have realized its great importance until Plummer³ announced his brilliant results at the meeting of the Association of American Physicians in May, 1923. On the basis of his theory that Graves' disease is associated with an alteration in the nature of the thyroid secretion he administered to a series of patients Lugol's solution (liquor iodi compositus) which contains 5 per cent iodine and 10 per cent potassium iodide. The dose now used is 10 to 15 drops well diluted in water once a day though the dose may be repeated three or four times a day for a few days if rapid results are needed in a crisis. It may be given by rectum during attacks of nausea and vomiting. Plummer and Boothby⁴ have reported on their results in 600 cases so treated at the Mayo Clinic. No patient has been made worse, all but about 5 per cent have improved. In a series of 43 patients carefully studied by means of basal metabolism tests one-third improved promptly and markedly, one-third improved definitely but not so markedly and one-fourth improved but slightly. In the cases that did well there was a steady fall in metabolism with corresponding improvement in symptoms until at the end of about two weeks the heat production was within the normal limits. When operation was performed during this iodine remission the mortality was less than 1 per cent. Following the thyroidectomy the Lugol's solution was continued for a few days and

¹ Crile: Jour. Am. Med. Assn., 1921, 77, 1324.

² Loucks: Am. Jour. Roentgenol., 1923, 10, 767.

³ Plummer: Jour. Am. Med. Assn., 1923, 80, 1955.

⁴ Plummer and Boothby: Jour. Iowa State Med. Soc., 1924, 14, 66.

the patients made unusually rapid recoveries. An illustrative chart is shown in Fig. 65.

This work of the Mayo Clinic has been fully confirmed by Starr, Segal and Means¹ in Boston and also by Mason of Montreal² and Read³ of California and by Fitzgerald.⁴ Means and his associates followed 42 patients, giving 15 drops of Lugol's solution a day. Eighty per cent of the cases showed

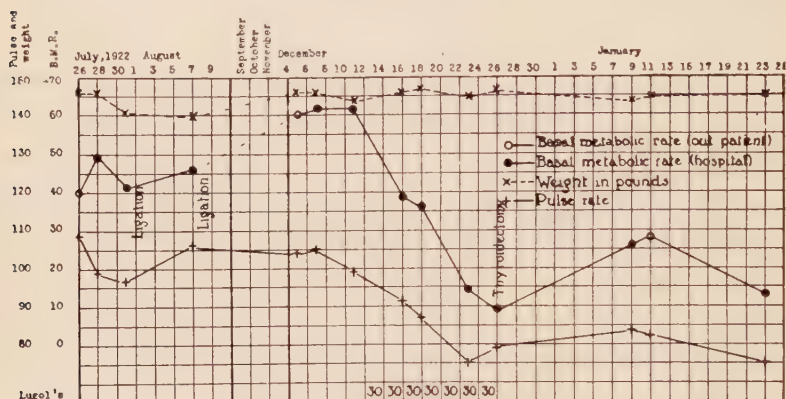


FIG. 65.—The effect of Lugol's solution in exophthalmic goiter. (Plummer and Boothby.) A woman, aged thirty-seven years, had been suffering from enlargement of the thyroid for three years with marked constitutional symptoms for two years. There was a loud bruit, exophthalmos, marked loss of weight and strength and moderate edema. Two ligations had been performed. The patient was followed for a week before the treatment with Lugol's solution was begun. During this time her basal metabolism was stationary at about 60 per cent above the normal. Coincident with the administration of the iodine the metabolism fell reaching the upper normal limit in fifteen days.

rapid improvement, the fall in metabolism following almost exactly the same curve as after subtotal thyroidectomy as is shown in Fig. 66. In 5 cases the metabolism fell almost to normal and then rose again although the drug was still being taken (Fig. 67). In other cases there was a prompt recurrence of symptoms as soon as the iodine was stopped. The Mayo Clinic and Boston investigators seem to employ iodine chiefly as a means of obtaining a remission during which an operation can be performed with comparative safety and with

¹ Starr, Segal and Means: Arch. Int. Med., 1924, 34, 355.

² Mason: Canad. Med. Assn. Jour., 1924, 14, 219.

³ Read: Endocrinology, 1924, 8, 746.

⁴ Fitzgerald: Canad. Med. Assn. Jour., 1926, 16, 159.

every expectation of cure. Mason and Read who have both observed the rapid fall in metabolism after Lugol's solution

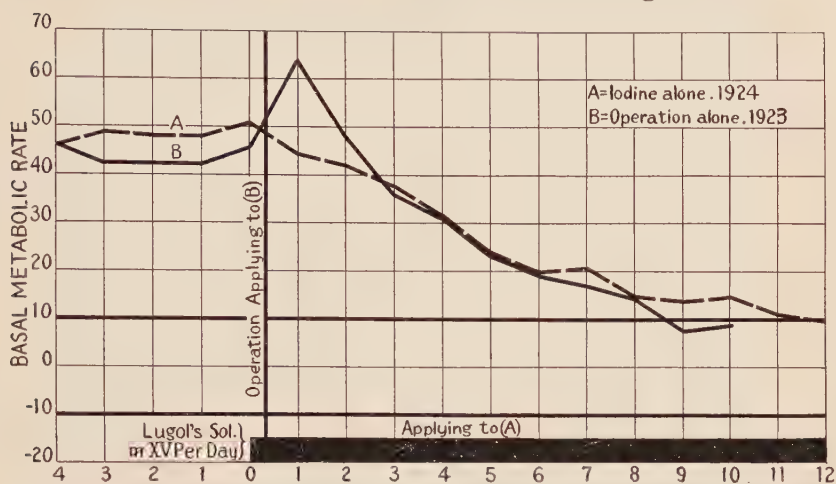


FIG. 66.—Comparison of the curves of detoxication after Lugol's solution and after subtotal thyroidectomy. The continuous line is the average curve obtained by Segall and Means following subtotal thyroidectomy, the interrupted line is the average obtained during the first few weeks of iodine therapy by Starr, Segal and Means.

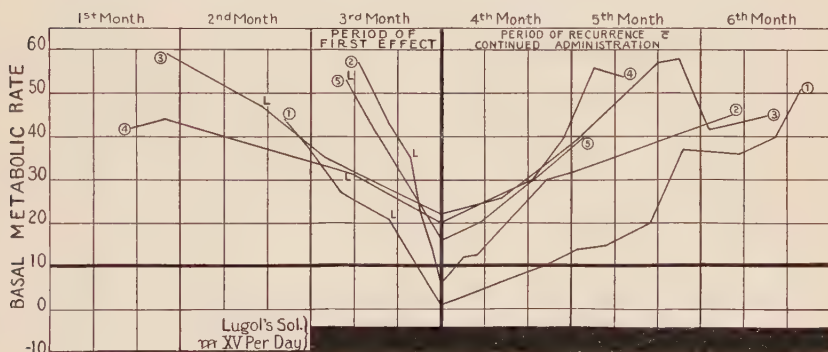


FIG. 67.—Remission and recurrence under iodine. Five metabolism curves, the remission being shown by the fall of the metabolic rate to the central ordinate. The compound solution of iodine was started in the individual cases at L. The recurrence is shown by the rise in the metabolism curves during the succeeding three months. (Starr, Segal and Means.)

have apparently been able to prolong the good effect by continued small doses. Mason says that the days of ligations are over. An interesting presentation of the whole subject

with an excellent discussion by Lahey will be found in the paper of the Boston Committee¹ investigating thyroid diseases.

Operative Treatment.—Statistical reviews of operation in thyroid disease must be made with great caution. It is obviously unfair to compare operations by the average surgeon with those of the masters of technic who operate continually on the gland. Not only is the operator important but also the anesthetist and the whole discipline of the hospital. In certain places an operation can be performed with

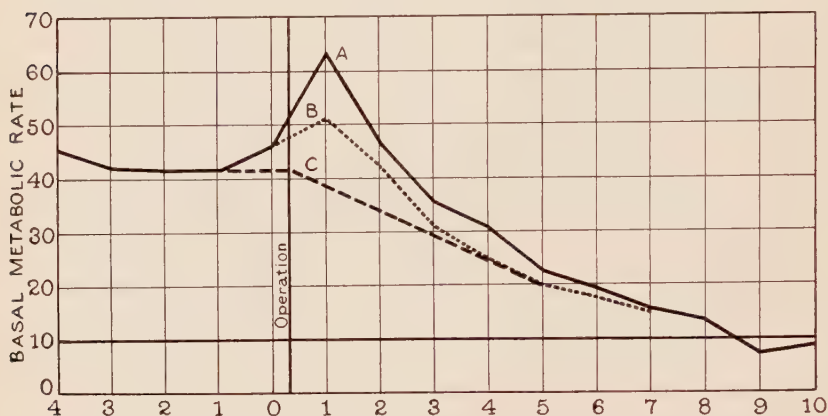


FIG. 68.—True detoxication curve after thyroidectomy. The solid black line A is the composite basal metabolism curve. From this is subtracted the effect that may be expected to be due to fever, shown by the dotted line B. The true detoxication curve may be expected to assume approximately the positive shown by the interrupted line C. The perpendicular distance between A and B thus represents the increase in calories due to fever, that between B and C the increase due to emotion and all other causes. (Segall and Means.)

comparatively little excitement and discomfort on the part of the patient. In other places any operative procedure, even though slight, combines all the factors calculated to cause an acute exacerbation in all the symptoms.

Depending, therefore, on the nature of the operation and the reaction of the patient, there is a tendency toward more or less increase in the thyrotoxicosis during and immediately after any operation and this is reflected by a rise in the basal metabolism well shown in the curve taken from the work of Segall and Means² (Fig. 68). The factors which produce

¹ Holmes, Means, Porter, Richardson, and Starr: Boston Med. and Surg. Jour., 1924, 191, 295.

² Segall and Means: Arch. Surg., 1924, 8, 176.

this are apprehension on the part of the patient, anesthesia, the trauma to the thyroid gland, fever, the oozing of blood, and the discomfort of recovery from anesthesia and from the pain in the wound.

Ligation.—The simplest of all operative procedures is ligation of one or two of the thyroid arteries. Ligation is now employed chiefly as a preliminary to the removal of a portion of the gland in cases that are suffering from severe symptoms. Boothby¹ gives an interesting table showing the average results of various methods of operative treatment. It will be seen that ten days after one or two ligations metabolism has dropped on an average 17 per cent in one group and 21 per cent in another, the larger drop occurring when only one ligation has been made. These decreases are probably rather more marked than would occur with rest alone.

Thyroidectomy.—After subtotal thyroidectomy in exophthalmic goiter the fall in metabolism is also demonstrated in the curve of Segall and Means. They have noted a rise in heat production just before the operation and this they ascribe to apprehension with a possible increase in the liberation of epinephrin. The peak of the curve which comes a day after operation they have shown to be coincident with and largely due to fever. When the factors of apprehension and fever have subsided by the third day the curve shows the true rate of detoxication and this is very similar to the rate of fall on the administration of iodine and the rate of fall observed by Aub and Stern² in a normal woman when they stopped the large doses of thyroid extract that had been given by another physician. Boothby³ has studied similar curves of the "rate of decay" after stopping thyroxin in myxedema. In studying the table given by Boothby (Table 70) we must remember that the milder cases have a primary thyroidectomy and the severer cases thyroidectomy after preliminary ligation. The operative removal of a large portion of the thyroid greatly lessens the degree of hyperthyroidism and in many cases results in a cure. The surgeons avoid operating during a rising curve of intensity, since there is a much greater surgical risk at this time. The curve of the basal metabolism affords one of the best means of determining the degree of intensity

¹ Boothby: Oxford Med., rewritten, 1923, 3, 935 (Table 13).

² Aub and Stern: Arch. Int. Med., 1918, 21, 130.

³ See Kendall: Indust. and Eng. Chem., 1925, 17, 525.

TABLE 70.—EFFECT OF OPERATIVE TREATMENT ON 284 CASES OF EXOPHTHALMIC GOITER AND ADENOMA. (BOOTHBY.)

	Exophthalmic goiter.						Adenoma.					
	Two ligations, at home, and thyroidectomy.			One ligation and thyroidectomy.			Primary thyroidectomy.			With hyperthyroidism.		
	Before treatment.	Ten days after second ligation.	After two months' rest.	After thyroidectomy.	Before treatment.	Ten days after first ligation.	After thyroidectomy.	Before treatment.	After thyroidectomy.	Before treatment.	After thyroidectomy.	Without hyperthyroidism.
Metabolism	+68%	+51%	+43%	+20%	+60%	+39%	+17%	+36%	+8%	+35%	+6%	-9%
Syst. blood-pressure . . .	139	132	131	125	137	126	119	133	122	145	133	115
Diast. blood-pressure . . .	75	72	72	75	71	66	71	73	73	81	78	70
Pulse-pressure	64	60	59	50	66	60	48	60	49	64	55	45
Pulse-rate	122	114	108	93	116	106	92	107	86	102	79	73
Weight	53.3	48.0	56.6	56.3	52.8	49.7	50.7	53.3	52.9	102	79	73
Number of cases in each group	55						42	72	92	23		

of the process. The extent of the operation and decision as to preliminary ligations or the amount of gland to be removed is, to a certain degree, influenced by the basal metabolism findings, but they should be considered merely as one part of the evidence.

The possibility of an operative fatality must be considered, though this is very rare in some clinics. Crile,¹ in 500 thyroidectomies previous to 1921, found a mortality of only 1 per cent; in 500 ligations, only 0.4 per cent.

In adenoma with hyperthyroidism Boothby's table shows a return of the metabolism to the normal limits. This usually

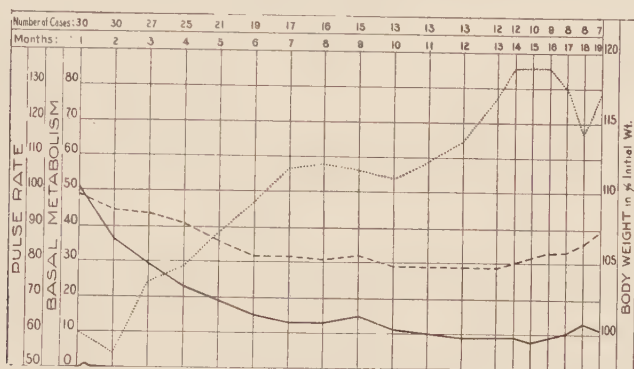


FIG. 69.—Exophthalmic goiter composite chart, 30 consecutive cases, subtotal thyroidectomy: Solid black line denotes metabolism; interrupted line, pulse; dotted line, weight. In this figure the curves begin at the time of the first operative procedure; the averages used as a starting-point are those obtained at the last metabolism determination before operation. This preceded operation by a variable period which is not shown. The time in months should begin with zero and not with 1. (Richardson.)

occurs within a comparatively few days and, as a rule, there is a complete cure. The removal of an adenoma in which there has been no hyperthyroidism causes but little change in the basal metabolism. Myxedema may follow any operation in which too large a portion of the thyroid gland is removed. Tetany follows only if the parathyroids are removed also.

E. P. Richardson² has made composite charts showing the results after subtotal thyroidectomy with the removal of three-quarters of the gland (Fig. 69). In the mild cases this was accomplished in one operation. In the severer

¹ Crile, S. W.: Jour. Am. Med. Assn., 1921, 77, 1324.

² Richardson: Jour. Am. Med. Assn., 1923, 80, 820 (Charts 2 and 3).

cases a series of graded operations was employed, removing in stages all of the gland except an amount which in the surgeon's judgment was necessary to maintain normal thyroid function. As a rule the inner posterior portions of both lobes were saved.

ILLUSTRATIVE CASES. — We shall select from the literature a few patients with exophthalmic goiter that have been studied in great detail. The first is from the Sage report of 1916.¹

History. — Max W., aged forty years, a Hebrew born in Roumania, was refused life insurance in 1912 because he weighed 190 pounds. In January, 1913, he received news that his brother had been murdered and he was greatly excited for a week. The next month he suffered from nervousness, loss of weight, and a severe unproductive cough. He was treated first for tuberculosis, then for syphilis, since the Wassermann reaction was found to be positive. It is fortunate that his doctors did not discover the traces of sugar in his urine or they would have treated him for diabetes. Eventually the diagnosis of exophthalmic goiter was made and he went to several hospitals, was turned out on account of his quarrelsome nature, and was finally transferred to Bellevue. On his admission on February 11, 1914, he weighed 62 kilograms, was 173.7 cm. tall, with classical angry facies and moderate exophthalmos. The thyroid was distinctly enlarged, especially the right lobe, the heart action rapid and regular, the skin warm and moist, the hands sweating and tremulous. At first he was treated with rest in bed. (On March 18, a period unfortunately not covered in the metabolism experiments, he developed an acute tonsillitis.) After March 5 he was treated with Beebe's serum with 1 grain of potassium iodide twice a day. He improved somewhat and left the hospital in April, 1914. Dr. Beebe continued his treatment, and during the next year Max gained 22 pounds and was able to work in his store. On April 22, 1915 he spent another day in the metabolism ward and went into the calorimeter again. His metabolism was unchanged, he was less excitable and seemed stronger, but the heart was fibrillating and was distinctly enlarged. In Figs. 70 and 71 are shown the results in graphic form. When he entered the hospital his metabolism was about 75 per cent above the normal, four days later it had dropped to +60 per cent, and by

¹ Du Bois: Clin. Cal. 14, Arch. Int. Med., 1916, 17, 915.

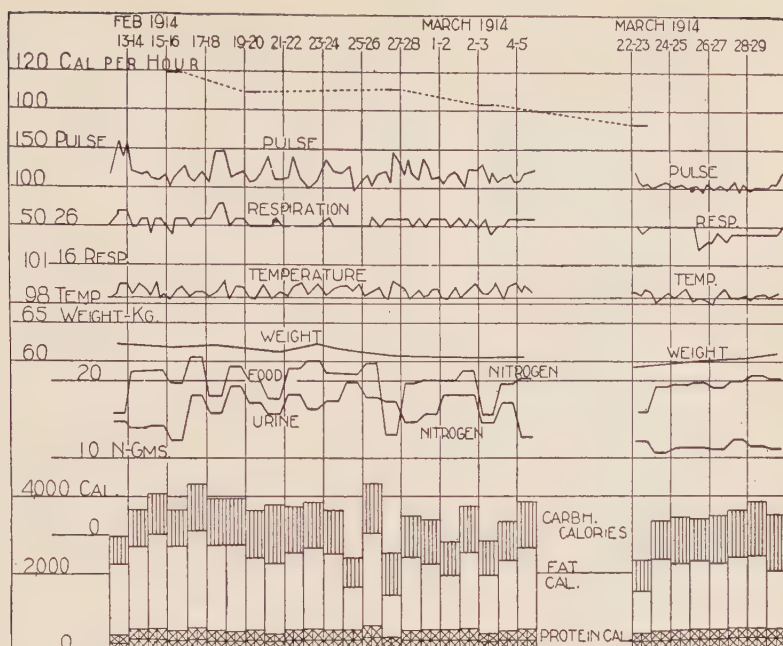


FIG. 70.—Max W.

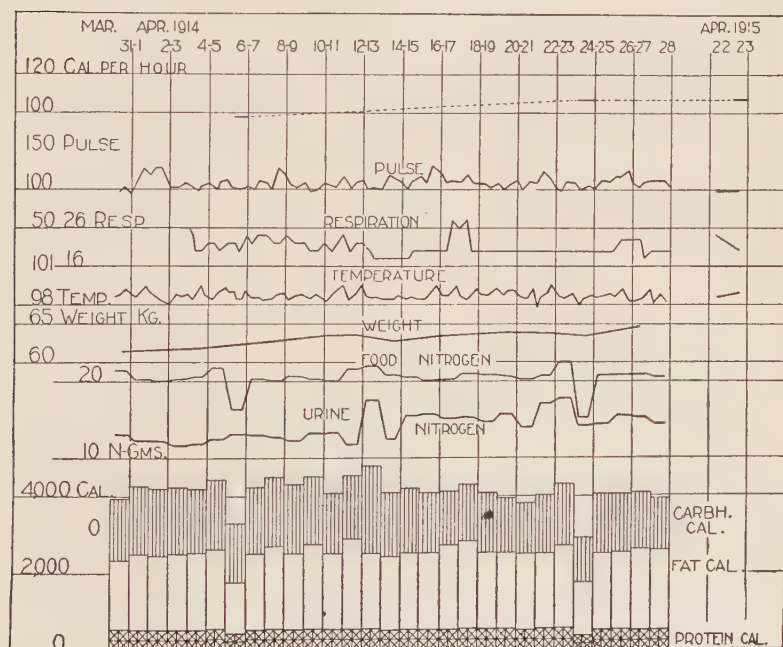


FIG. 71.—Max W.

April 6 it was down to +44 per cent. It is extremely doubtful if the serum had any therapeutic action.

He produced about 110 calories an hour while in the calorimeter and his specific dynamic action, as estimated in a few experiments, seemed to be within normal limits. When not in the calorimeter he was somewhat restless. His basal metabolism would amount to 2640 calories a day, but his weight remained constant while he was receiving almost 4000. In April, with a lower basal metabolism, the weight increased steadily on a diet of over 4000 calories. During February the food nitrogen exceeded the urine nitrogen by 4 to 7 grams a day, and the feces nitrogen averaged 3.7 grams a day. During April the nitrogen retention was apparently much greater. Such balances are probably not exact, however, unless the sweat and feces nitrogen are determined over a long period. When he returned after a year's treatment at home he produced the same number of calories as before, but on account of his greater weight, the percentage of increase above the normal was a little lower.

Patient of Sturgis.—The most complete report in the literature is that of Sturgis.¹ For one hundred and ninety-two consecutive days he determined the basal metabolism and food intake. The case report is as follows:

History.—An Irish woman, aged thirty-two years, had always been strong and healthy except for severe attacks of tonsillitis almost every year. She had been married thirteen years, had two children, took care of her own family, and did extra work as a laundress in order to make both ends meet. Six months before admission she became unusually tired and nervous and suffered from attacks of weeping. She also noticed palpitation and moderate dyspnea and lost 30 pounds in spite of a hearty appetite. She felt warm and used few bed clothes. Later she developed puffiness under the eyes. In spite of marked symptoms she kept at her laundry work. On admission it was found that she had a moderate enlargement of the thyroid, a warm, moist skin, tremor of the fingers, no outspoken exophthalmos. The heart was somewhat enlarged. She was admitted on March 1 and treated by complete rest. From March 13 to 18 she suffered from an acute tonsillitis with a mouth temperature rising to 102.2° F.

¹ Sturgis: Arch. Int. Med., 1923, 32, 50.

Between April 15 and June 13 she was given four roentgen-ray treatments. On July 27 and 31 the superior thyroid arteries

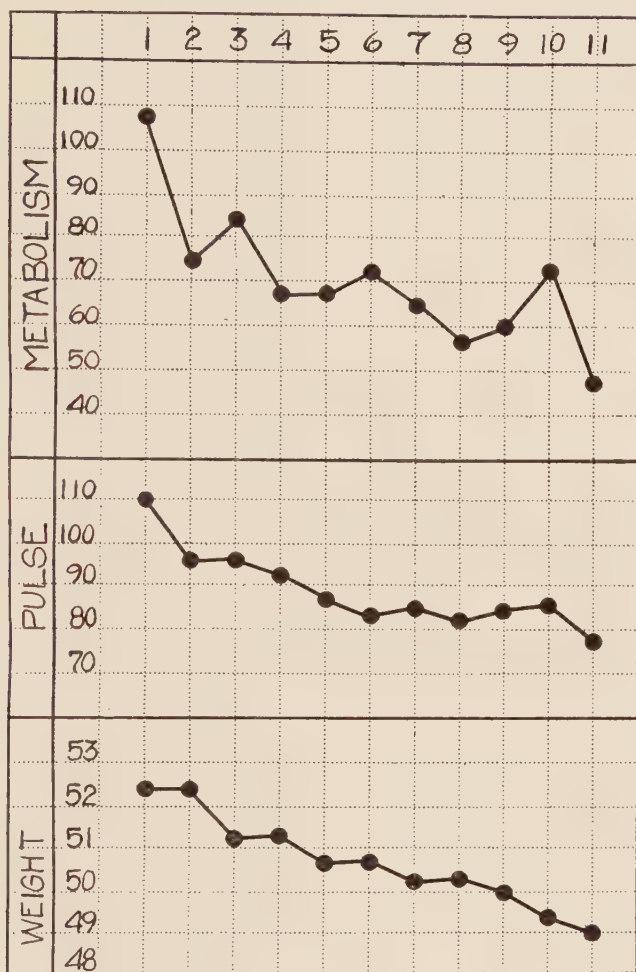


FIG. 72.—The basal metabolism in per cent of the average normal person, resting pulse-rate per minute and body weight in kilograms for the first eleven days in the hospital. Note the difference (34 per cent) between the determinations on the first and second days, and also the difference (23 per cent) between the determinations on the tenth and eleventh days. (Sturgis.)

were ligated one at a time. Thyroidectomy was attempted on August 16 but was abandoned on account of an unfavorable reaction toward anesthetization. Six days later a successful

operation was performed under local anesthesia and for several days she was in an extremely precarious condition. She was discharged from the hospital on September 19 much improved.

One hundred ninety-two basal metabolism determinations were made. Of the duplicate tests on each morning 81 per cent were within 3 per cent of each other and 94.5 were within 5 per cent of each other. This shows extraordinarily accurate work. Fig. 72 gives the marked fall in metabolism during

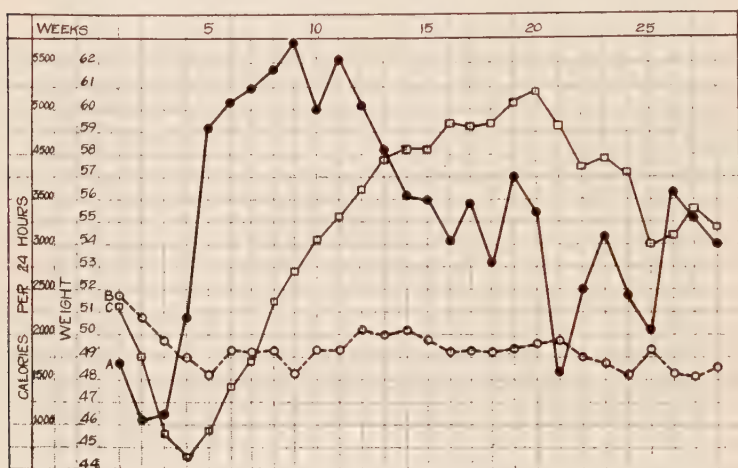


FIG. 73.—Relationship between the average twenty-four-hour caloric intake and expenditure and body weight per week for twenty-eight weeks. *A*, number of calories in the form of food consumed by the patient; *B*, energy expenditure per twenty-four hours calculated from the basal metabolism, to which has been added 10 per cent of the total caloric intake for the specific dynamic action of food, and 15 per cent for additional movements while the patient was resting in bed; *C*, body weight in kilograms. The average weekly energy expenditure remained fairly constant throughout the entire observation period, while the body weight, which varied widely, was directly proportional to the amount of food consumed. (Sturgis.)

the first eleven days, Fig. 74 the effect of fever due to tonsillitis. Roentgen-ray treatment in this case had no beneficial effect. Fig. 75 shows the slight fall following ligation; Fig. 76, the marked rise after thyroidectomy and the subsequent fall almost to normal. There was no consistent change in metabolism during six menstrual cycles.

Of especial interest are the curves given in Fig. 73, showing the relationship between body weight, basal metabolism, and food intake. Sturgis, following the method of calculation

used for most patients in bed, added to the basal metabolism 10 per cent for the specific dynamic action of food and 15

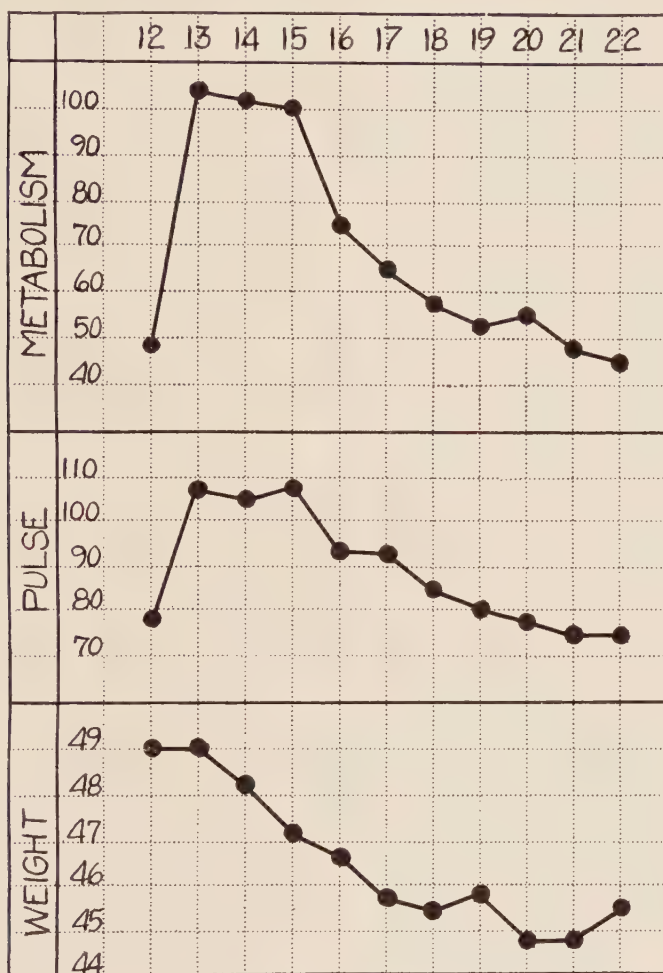


FIG. 74.—The effect of an acute tonsillitis with fever on the daily basal metabolism, resting pulse-rate and body weight. The patient developed fever on the thirteenth of the month, which persisted until the seventeenth. The increase in the metabolism was approximately proportional to the degree of fever. The changes in the resting pulse corresponded to the variations in the basal metabolism. The decrease in body weight resulted from an increase in the metabolism and a diminished food intake. (Sturgis.)

per cent for additional movements in bed. Calculated in this manner, the average daily need for a period of twenty-

eight weeks was 2349 calories, the average food ingested 3953 calories. The patient gained 3.4 kilograms in weight in twenty-eight weeks, and Sturgis calculates an average storage of 132 calories daily. Allowing for a loss of 362 calories in the feces, we have a surplus of 1110 calories unaccounted for, or 59 per cent of the average basal metabolism. This probably means that, instead of allowing 15 per cent for additional movements of the patient in bed, we should allow 74 per cent. This, added to the amount for the specific dynamic action, makes a total of 84 per cent, a figure in close agree-

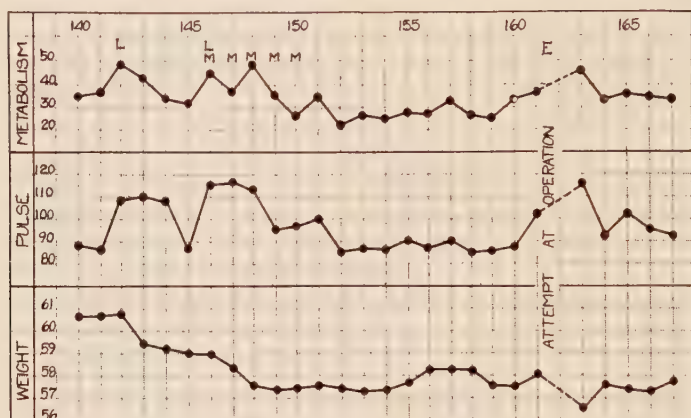


FIG. 75.—The effect of ligation of two thyroid arteries on the basal metabolism, pulse-rate and body weight. The metabolism is expressed in percentage of normal, the pulse in beats per minute, and the body weight without clothing in kilograms. *L*, indicates ligation of a thyroid artery; *M*, days during which the patient was menstruating; the figure at the top of the chart indicates the number of days the patient had been in the hospital; *E*, the day on which the patient was completely anesthetized but not operated on on account of the unfavorable reaction following the administration of the ether. (Sturgis.)

ment with that of Boothby,¹ who suggests that at least 75 per cent be added to the basal metabolism to meet the dietary requirement of this disease. Sturgis and Greene² in later studies find that their patients with exophthalmic goiter require 75 to 100 per cent of the basal calories for these extra needs.

Sturgis found that the fever of tonsillitis caused an increase in metabolism fairly closely proportional to the level of the

¹ Boothby and Sandiford: *Med. Clin. North America*, 1921, 5, 425.

² Sturgis and Greene: *Arch. Int. Med.*, 1925, 36, 561.

body temperature. Before the attack the metabolism was 49 per cent above the average normal; with a temperature of 102.2° F. by mouth the metabolism was 104 per cent above normal. After the operation under local anesthesia the metabolism rose from +32 to +75 per cent the next day.

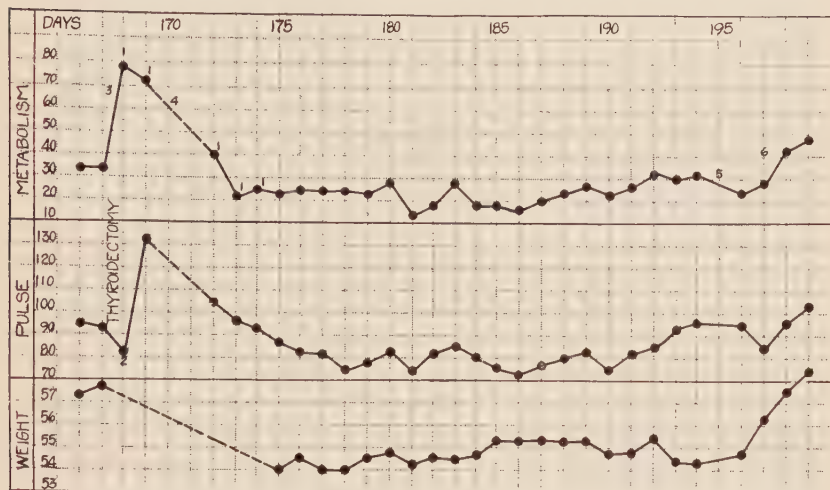


FIG. 76.—The effect of removal of approximately one-half of the thyroid gland on the basal metabolism, resting pulse-rate per minute and body weight. 1, the body weight on the day previous to the operation was used in estimating the surface area. 2, the pulse-rate at the wrist was 82 per minute, while that at the apex of the heart, while not counted, was much higher; the pulse deficit was due to many extrasystoles. 3, about one-half of the thyroid gland was removed under local anesthesia. Approximately one hour after the conclusion of the operation the patient's expired air was collected for one six-minute period. 4, the patient was too ill to make metabolism determinations on the second and third postoperative days. 5, determination lost on account of technical error. 6, the last three determinations on the chart were made after the patient had returned home and was resting about half of the time in bed. She came to the hospital at weekly intervals for observation. (Sturgis.)

During the following two days the patient's condition was too serious to make the tests, but by the fourth day the acute hyperthyroidism had passed.

After the prolonged period of observation in the hospital the patient returned to her home and rested half of the day. She did not do very well, and the metabolism rose to +47 per cent again. On November 13 more of the thyroid gland was removed. Six days later the metabolism was +14 per cent.

Aub and Stern's Case.—Aub and Stern¹ report an unusual case of great interest. Miss C. E. A., was a violin teacher aged twenty-four years. Her heart rate had always been slow, usually 50. She had occasional pains in the heart region. Having had symptoms suggestive of myxedema seven years previously, she had been treated with thyroid extract from time to time, and in June, 1916, her family physician decided to push the drug until symptoms appeared. He gave as much as 26 to 28 grains of Burroughs, Wellcome & Company's thyroid tablets a day and continued this for over a month. There was no tachycardia and the pulse was seldom over 62. There was no headache, exophthalmos, diarrhea, sweating, or loss of weight. The thyroid was not enlarged. There was only a slight tremor.

On admission to the hospital the drug was continued and the metabolism was found to be established at 41 to 47 per cent above the normal. The electrocardiogram showed complete auriculo-ventricular dissociation, which explained why she did not develop tachycardia. On the twelfth day after stopping the thyroid extract the basal metabolism was +11; on the nineteenth day +3.

¹ Aub and Stern: Arch. Int. Med., 1918, 21, 130.

CHAPTER XIV.

BASAL METABOLISM AND THE ADRENAL, PITUITARY AND SEX GLANDS.

ADRENALS.

AUB, Forman and Bright,¹ in 1922, collected from the literature and from personal communications the reports on basal metabolism in Addison's disease. Loeffler² records the case of a woman, aged thirty-nine years, who, on entrance to the hospital, gave a reading 26.5 per cent below the average normal of the Sage standards. Two months later, a week before death, her metabolism was 20 per cent below the normal. The autopsy showed tuberculosis of both adrenals with caseation. Muirhead³ reports a case of Addison's disease 30 per cent below normal. An unpublished case of Means⁴ is quoted at -15 per cent, and one of Christian and Sturgis⁵ showed a metabolism 12 per cent below the average in spite of restlessness during the entire experiment. On autopsy the adrenals in this case showed caseous tubercular nodes with only a few strands of cortical adrenal cells intact. Boothby and Sandiford,⁶ in a preliminary report, list the results in 13 cases of Addison's disease. One showed metabolism greater than +20 per cent above normal, 2 were below -20 per cent, 1 was between -11 and -15 per cent, and the others were within the normal limits. The details of these cases will be awaited with interest. Considering the wasting and asthenia that characterizes Addison's disease, we should expect a lowered metabolism, but in some cases, previously reported, the lowering may be partly due to a specific absence of adrenal secretion. It is quite possible that a tendency toward lowering may be compensated in part by other factors which tend to raise metabolism.

¹ Aub, Forman and Bright: *Am. Jour. Physiol.*, 1922, **61**, 340.

² Loeffler: *Ztschr. f. klin. Med.*, 1919, **87**, 280.

³ Muirhead: *Jour. Am. Med. Assn.*, 1921, **76**, 652.

⁴ Means: Personal communication to Aub.

⁵ Christian and Sturgis: Personal communication to Aub.

⁶ Boothby and Sandiford: *Jour. Biol. Chem.*, 1922, **54**, 783.

In the Chapter on the Thyroid (p. 318) we have discussed briefly some of the work on the effect of epinephrin on the metabolism. The literature on this subject is voluminous, contradictory, and confusing. The reader who is interested in the details is referred to the excellent discussions in the reviews of McCann,¹ Boothby and Sandiford² and in Grafe's³ monograph. The latter believes that the high quotients after the administration of adrenalin are caused by a true increase in the oxidation of sugar, although in some cases part of the increase in quotient may be due to purely physical factors and other artifacts. He believes that the increase in metabolism following the administration of adrenalin is caused by an increase in the total vital tonus, and that the increase in respiratory-circulatory nervous factors and the light tremor occasionally encountered are the expression of the general cellular irritation or stimulation. Boothby and Sandiford⁴ speak of it as a calorigenic action. Grafe believes that the increase in total metabolism following adrenalin is not associated with any increase in protein metabolism, this latter appearing as a rule only in starvation or undernourishment and under the exhibition of large toxic doses. Likewise, he finds no evidence for the toxic destruction of protein in Addison's disease.

PITUITARY DISEASE.

Snell, Ford and Rowntree⁵ have reported on several cases of pituitary disease, as will be seen in Table 71.

Tierney⁶ has studied a number of cases of hypo- and hyperpituitarism. Boothby and Sandiford⁷ show that in their series of 30 cases of acromegaly the majority were within 15 per cent of the average normal, 1 was below normal, 8 were more than 20 per cent above. Some of this last group may have suffered from a complicating hyperthyroidism. In 58 cases of hypopituitarism most of the cases were also within 15 per cent of the normal, but about a third of them showed

¹ McCann: *Calorimetry in Medicine*, Williams & Wilkins Company, Baltimore, 1924, p. 47 and p. 55. (Also in *Medicine*, 1924, 3, 1.)

² Boothby and Sandiford: *Physiol. Rev.*, 1924, 4, 69.

³ Grafe: *Ergeb. d. Physiol.*, 1923, 21, Part II, 1.

⁴ Boothby and Sandiford: *Am. Jour. Physiol.*, 1920, 51, 200.

⁵ Snell, Ford and Rowntree: *Jour. Am. Med. Assn.*, 1920, 75, 515.

⁶ Tierney: *Med. Clin. North America*, 1920, 4, 775.

⁷ Boothby and Sandiford: *Jour. Biol. Chem.*, 1922, 54, 783.

distinct depression of metabolism. Labbé, Stevenin, and van Bogaert¹ noted a striking increase in metabolism in 2 patients with typical acromegaly and normal or slightly lowered figures in 3 cases of slight acromegaly. Talbot² in the case of one very obese child with a small sella turcica found the metabolism about 40 per cent lower than that of boys of the same weight or the same surface.

Plaut³ has reported on the basal metabolism and specific dynamic action of food in 10 patients with hypophyseal obesity and hypophyseal cachexia. In all but 2 the basal figures were within 10 per cent of the average normal, 1 showed +30 per cent, another -16 per cent. The rise in metabolism after food was rather less than in the normal controls.

We see that there is no great uniformity in diseases of the pituitary. There is some evidence of an increase in metabolism in the early stages of acromegaly, but Boothby⁴ says, "There is, however, as yet little evidence that the secretion of any part of the pituitary gland is concerned with the normal rate of cellular combustion in the sense that it acts as a calorogenic agent."

Bernstein and Falta⁵ studied the gaseous exchanges after giving pituitary extracts. They found pituitrin from the pars nervosa caused a rapid rise in oxygen consumption with no change in respiratory quotient. A protein-free extract of the glandular portion of the pituitary caused a fall in metabolism lasting about an hour, with a transient rise in the respiratory quotient. McKinlay⁶ gave to 12 normal controls 1 cc of pituitary extract of the posterior lobe and pars intermedia. Eleven of them showed an increase in metabolism varying between 7 and 16 per cent, averaging 5 per cent. In 4 cases of hypothyroidism there was no rise. In 3 cases with pituitary disturbance and low metabolism pituitrin caused an increase. In another group of 4 normals and 2 hypothyroids, thyroxin was given and one week later pituitrin. Normals reacted with increased heat production; myxedematous patients did not.

¹ Labbé, Stevenin, and van Bogaert: *Ann. de Med.*, 1925, **17**, 258.

² Talbot: *Am. Jour. Dis. Child.*, 1920, **20**, 331.

³ Plaut: *Deutsch. Arch. klin. Med.*, 1922, **139**, 285.

⁴ Boothby: *Jour. Am. Med. Assn.*, 1921, **77**, 252.

⁵ Bernstein and Falta: *Verhandl. d. Deutsch. Kong. f. inn. Med.*, 1912, **29**, 536; *Deutsch. Arch. klin. Med.*, 1918, **125**, 233.

⁶ McKinlay: *Arch. Int. Med.*, 1921, **28**, 703.

TABLE 71.—BASAL METABOLIC RATE IN PITUITARY DISEASES. (ROWNTREE.)

No.	Patient.	Age.	Sex.	Diagnosis.	Date; initial rate.	Treatment.	Rate while under treatment.	Comment.
1	L. K., 18731	33	♀	Diabetes insipidus	Mar. 13, 1920: +30 Apr. 18, 1920: -8	Pituitary extract by hypo- dermic	Mar. 20, 1920: +5 ¹ Apr. 20, 1920: +1.3	Urine reduced from 11 to 3.5 liters.
2	H. O., 293184	30	♂	Diabetes insipidus	Mar. 31, 1920: -10	Pituitary extract	Apr. 19, 1920: -4	Urine reduced from 10 to 2 liters.
3	C. M.	30	♀	Diabetes insipidus	Apr. 3, 1920: -1	Pituitary extract	Apr. 19, 1920: -1	Urine reduced from 10 to 2 liters.
4	H. N.	28	♂	Diabetes insipidus	Apr. 3, 1920: -1	Pituitary extract	Apr. 19, 1920: -1	Urine reduced from 12 to 2.5 liters.
5	M. L., 18614	53	♀	Diabetes insipidus	Mar. 30, 1920: +20	Pituitary extract by hypo- dermic; posterior lobe feeding	Mar. 26, 1920: +10 ¹ Apr. 3, 1920: +3.8	Urine reduced from 9 to 1.5 liters.
6	E. T., O. P.	20	♀	Fröhlich's syndrome	Mar. 7, 1920: +1.6	Anterior lobe feeding; 5 grains 3 times daily for 10 days	Apr. 11, 1920: -1.2	
7	L. T. B., O. P.	24	♂	Fröhlich's syndrome	Dec. 15, 1919: -1.2	Anterior lobe, 45 grains a day; thyroxin, 2 mg. every 3d day for 5 doses; anterior lobe feeding 45 grains a day; thyroxin, 2 mg. every 3d day for 5 doses	Jan. 10, 1920: -2.2 Feb. 11, 1920: +53.4 Feb. 25, 1920: -5 Mar. 29, 1920: +35.4	

¹ The marked fall from the initial level may have resulted from confining the patient to bed.

The Influence of the Sex Glands on Basal Metabolism.—In the Chapter on Normal Metabolism we have discussed the fact that women show a basal metabolism lower than that of men. Heat production is on a lower plane, both on the basis of body surface and unit of body weight. This difference between the two sexes is quite manifest after the first year of life and is fully established by the age of puberty. After this period the zone between the two sexes remains at about the same width, the average curves being separated by 6 to 7 per cent. Of course, many normal men show figures below the average for women and many normal women are above the average for men.

Part of the difference can be explained by the greater proportion of fat in the bodies of women and by the fact that on the average they do not perform as much muscular exercise as men. As we have said before, this does not explain the lower metabolism of young girls who are about as active as their brothers. Perhaps we are right in ascribing some of the difference to the sex glands. Unfortunately, we know comparatively little about the metabolism at the two great sex epochs, puberty and the menopause. We have discussed puberty under the subject of metabolism in childhood. There seems to be an increase at this period in certain individuals, due perhaps to abnormal thyroid activity, perhaps to the interstitial glands themselves. The menopause has never received the attention it deserves. Harris and Benedict¹ studied only one woman between the ages of forty-five and fifty-five years. Boothby's charts do not indicate any great departure from the normal curve at this age. Epstein and Lande² studied 10 women at the menopause and found 2 with figures between 12 and 15 per cent above the average normal according to surface area; 5 were between 3 and 10 per cent above; the rest were on the normal line.

So many women show a tendency toward obesity after the normal menopause that one is inclined to believe in a lowered metabolism. There seems to be no definite proof of such a decrease and the gain in weight may be due to other causes, such as a lessened muscular activity or disproportion between appetite and expenditure of calories. After an artificial menopause, however, there is evidence of a fall in metabolism.

¹ Harris and Benedict: Carnegie Institution of Washington Publication No. 279, 1919.

² Epstein and Lande: Arch. Int. Med., 1922, 30, 563.

Thus Kraul and Halter¹ noticed a diminution in heat production subsequent to removal of the uterus and an average fall of 20 per cent following roentgen-ray castration of women. Plaut and Timm² obtained similar depressions of rate from using roentgen-ray in castrating doses for myomas or hemorrhage. When the symptoms of the artificial menopause had passed the metabolism returned to normal. There seems to have been no particular fall in metabolism from the roentgen-rays in women who had already passed the menopause.

Lüthje,³ working with canines of both sexes, found no change in metabolism after castration. Zuntz⁴ studied 4 women before and after menopause following operation. Three showed no change; 1 whose metabolism was probably high on account of pus tubes, showed a drop of 20 per cent. The administration of ovarian extract caused no appreciable effect on the basal figures. Tierney⁵ describes a thin, eunuchoid woman, aged twenty-seven years, with a basal metabolism 13 per cent below the average. Zuntz⁶ found little change due to absence of sex glands, as did Falta⁷ in a case of traumatic eunuchoidism as a result of a war wound. Loewy and Kaminer⁸ report a moderate reduction of metabolism in a soldier who had lost his testes. The subject has been well reviewed by Grafe⁹ in his monograph, and we can agree with his conclusion that a total absence or diminished function of the sex glands only exceptionally causes a diminution in the oxidative processes.

This has recently been confirmed by the careful and comprehensive studies of J. T. King,¹⁰ of Baltimore. He measured the oxygen consumption of a large number of women over forty years of age and found that those with normal pelvic organs gave average figures which agreed closely with the Sage standards showing the same gradual drop in metabolism

¹ Kraul and Halter: *Ztschr. f. Geburts. u. Gynäk.*, 1924, **87**, 606; *Wien. klin. Wchnschr.*, 1923, **36**, 538.

² Plaut and Timm: *Klin. Wchnschr.*, 1924, **3**, 1664.

³ Lüthje: *Arch. f. exper. Pathol. u. Pharmakol.*, 1902, **48**, 184.

⁴ Zuntz, Leo: *Ztschr. f. Geburtsh. u. Gynäk.*, 1904, **53**, 352.

⁵ Tierney: *Med. Clin. North America*, 1920, **4**, 775.

⁶ Zuntz, L.: *Zentralbl. f. Gynäk.*, 1904, **28**, 1492; *Arch. f. Gynäk.*, 1912, **96**, 188.

⁷ Falta: *Die Erkrankungen der Blutdrüsen*, Berlin, Springer, 1913, p. 336.

⁸ Loewy and Kaminer: *Berl. klin. Wchnschr.*, 1916, **53**, 1123.

⁹ Grafe: *Ergeb. d. Physiol.*, 1923, **21**, Part II, 1.

¹⁰ King, J. T.: *Bull. Johns Hopkins Hosp.*, 1926, **39**, 303.

from decade to decade. Another group of women studied several years after hysterectomy, single or double oöphorectomy gave approximately the same averages. He concludes that there is no permanent change in the basal metabolism as a result of these operations. The gain in weight he believes to be accounted for by reduction in vigor. This same gain in weight is accompanied by an increase in basal metabolism which is more closely proportional to the gain in surface area than to any possible increase in "active protoplasmic mass."

The Influence of Menstruation.—Some women feel but slight discomfort at the menstrual periods and do not find it necessary to alter their activities. Others suffer pain and show a great deal of nervous irritability or exhaustion. We might infer that in such cases there would be a disturbance in the various endocrine secretions and perhaps an increased thyroid activity. For this reason we are naturally interested in possible changes in the basal metabolism.

Zuntz¹ studied 2 women for several months. One was a virgin whose menses were scant and accompanied by moderate dysmenorrhea. The other had a child one year old. Her menses were rather more profuse, but were accompanied by no pains. There were no consistent variations in the oxygen absorption or carbon dioxide excretion either before, during, or after the menstrual periods in these two women, but the temperature during these periods averaged 0.36° C. higher than in the premenstrual periods. Gephart and Du Bois² found no difference in the case of an artist's model who suffered no discomfort. She was studied on the second day of the catamenia and again four days later. Blunt and Dye³ found no definite change in basal metabolism or pulse-rate in a large number of observations on college women. The average of the menstrual days was only 1.6 per cent lower than at other times. On the other hand, Snell, Ford and Rowntree⁴ obtained evidence of an average increase of 10 per cent during the menstrual periods. Rowe and Eakin⁵ observed the same thing, but they also found that their men showed a similar fluctuation. Wakeham⁶ studied a

¹ Zuntz, Leo: *Arch. f. Gynäk.*, 1906, **78**, 106.

² Gephart and Du Bois: *Clin. Cal.* **13**, *Arch. Int. Med.*, 1916, **17**, 902.

³ Blunt, K., and Dye, M.: *Jour. Biol. Chem.*, 1921, **47**, 69.

⁴ Snell, Ford and Rowntree: *Jour. Am. Med. Assn.*, 1920, **75**, 515.

⁵ Rowe and Eakin: *California State Jour. Med.*, 1921, **19**, 320.

⁶ Wakeham: *Jour. Biol. Chem.*, 1923, **56**, 555.

number of healthy nurses and found rather large individual variations.

His results given in Fig. 77 indicate a premenstrual rise in metabolism. A similar rise before menstruation with an intermenstrual minimum about 5 per cent lower was observed by Hafkesbring and Collett¹ in their long and careful study of two women. Kunde² also noted a slight fall during

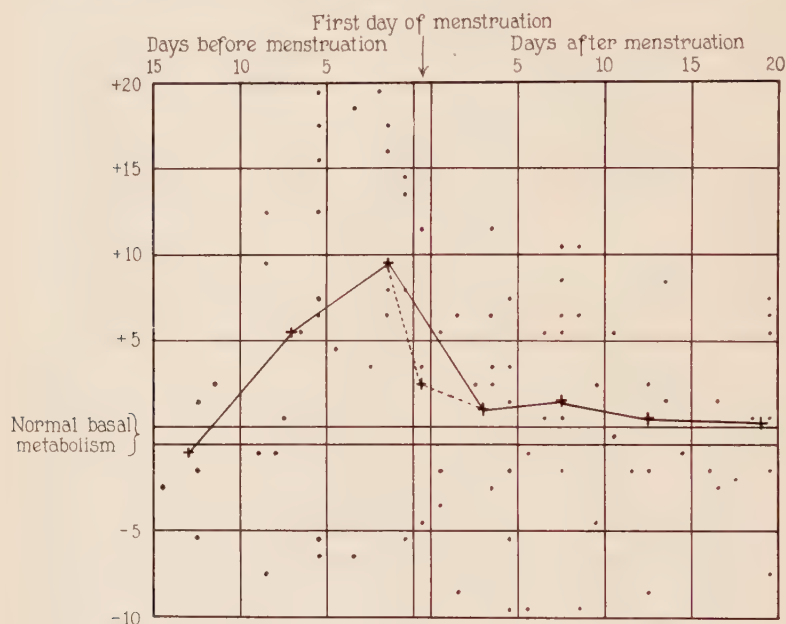


FIG. 77.—Chart showing scatter of individual observations with line for averages. (Wakeham.)

menstruation in one normal woman. Lanz³ says that in healthy women menstruation frequently does not influence the basal metabolism but in sick women there is an increase in the premenstrual period and a rapid fall after the onset. Wiltshire⁴ found no change in metabolism during the catamenia or alteration in the cost of work or rate of recovery from work. Sturgis did not encounter any menstrual variations in the heat production of the woman with exophthalmic goiter studied on one hundred and ninety-two

¹ Hafkesbring and Collett: *Am. Jour. Physiol.*, 1924, **70**, 73.

² Kunde: *Jour. Metab. Res.*, 1923, **3**, 399.

³ Lanz: *Ztschr. f. Geburtsh. u. Gynäk.*, 1925, **89**, 133.

⁴ Wiltshire: *Lancet*, 1921, *ii*, 388.

consecutive days and described on page 340. The subject is not yet settled in spite of all this labor. It would seem as if some women did have monthly variations in metabolism. Boothby and Sandiford¹ have observed that pain or distress whether of menstrual or other origin will cause a rise and we must therefore exclude this factor in estimating the effect of the sex glands.

Influence of Pregnancy.—During the first half of pregnancy the weight of the product of conception is negligible in comparison with that of the mother. Later there is a more rapid development of the fetus and also of the placenta and inert liquor amnii. Matters are still further complicated by changes in body weight and by a pressure upward on the diaphragm which increases the labor of respiration. There are also considerable variations in the habits of life and in muscular exercise. After parturition there are the new factors of involution of the uterus and development of the lacteal glands. It is difficult, therefore, to interpret the rather limited work on this subject.

Murlin² has discussed the question at length and has grouped the evidence in one table. Zuntz³ studied 3 women throughout the greater part of pregnancy. Two of them had served as subjects for his earlier work on menstruation. The figures were higher during the latter part of pregnancy. He believed that part, but not all, of this was due to the increased labor of respiration. Carpenter and Murlin⁴ studied 3 women before and after parturition and concluded that, per unit of body weight, the metabolism during the latter part of pregnancy was about 4 per cent higher than that of women at complete sexual rest. In the newly delivered woman they found an increase which they ascribed in part to the activity of the mammary glands and in part to the dynamic action of protein liberated by the involution process. Curiously enough they found that the energy production of the mother and child together a few days after parturition just about equaled that of the mother before confinement. The extra metabolism of the pregnant woman at the culmination of pregnancy, due in part to the accessory structures as well as to the fetus,

¹ Boothby and Sandiford: *Physiol. Rev.*, 1924, 4, 69.

² Murlin: *Endocrinology and Metabolism*, New York, D. Appleton & Co., 1922, 3, 621 (Table 24, p. 625).

³ Zuntz, Leo: *Arch. f. Gynäk.*, 1910, 90, 452.

⁴ Carpenter and Murlin: *Arch. Int. Med.*, 1911, 7, 184.

is just equaled by the extra metabolism set up in the new-born child by exposure of its body to the outside world, and in the mother by activity of the mammary glands, etc. This confirms the earlier work of Murlin¹ on the dog.

Root and Root² have made a beautifully detailed study of one pregnant woman, and the results are given in Fig. 78. In the fourth month of her first pregnancy the metabolism

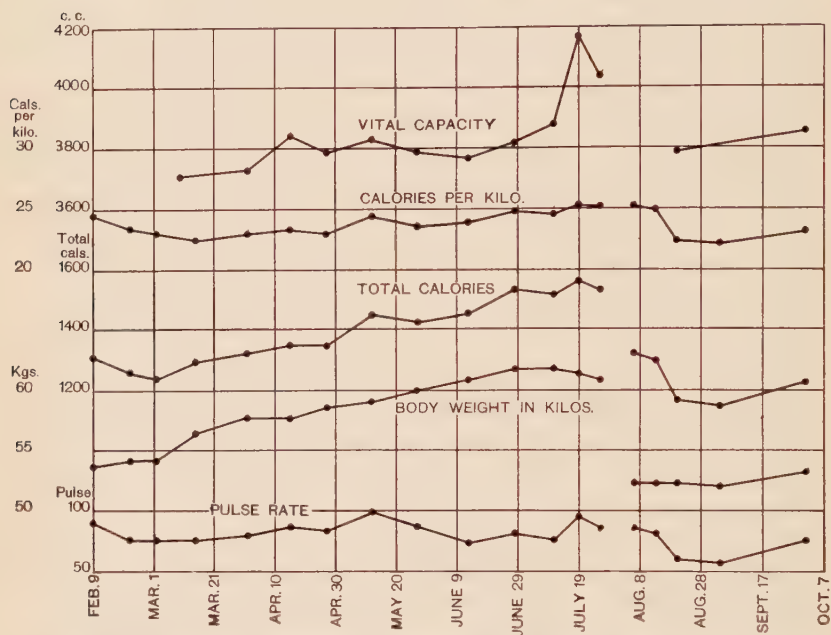


FIG. 78.—Curves for pulse-rate per minute, body weight, basal heat production per twenty-four hours and per kilogram per twenty-four hours, and vital capacity from the fifteenth week of pregnancy until the eighth weeks after delivery (July 31, 1922). (Root and Root.)

was 5.4 per cent below the Harris-Benedict standard. The basal metabolic rate increased slowly and rose out of proportion to the gain in weight. A few days before delivery it was 10 per cent above the Harris-Benedict standard, and following delivery, after remaining stationary for a time, fell gradually until it was about 10 per cent lower than in the fourth month.

Rowe, Alcott and Mortimer³ found a similar gradual rise

¹ Murlin: *Am. Jour. Physiol.*, 1910, 26, 134.

² Root and Root: *Arch. Int. Med.*, 1923, 32, 411.

³ Rowe, Alcott and Mortimer: *Am. Jour. Physiol.*, 1925, 71, 667.

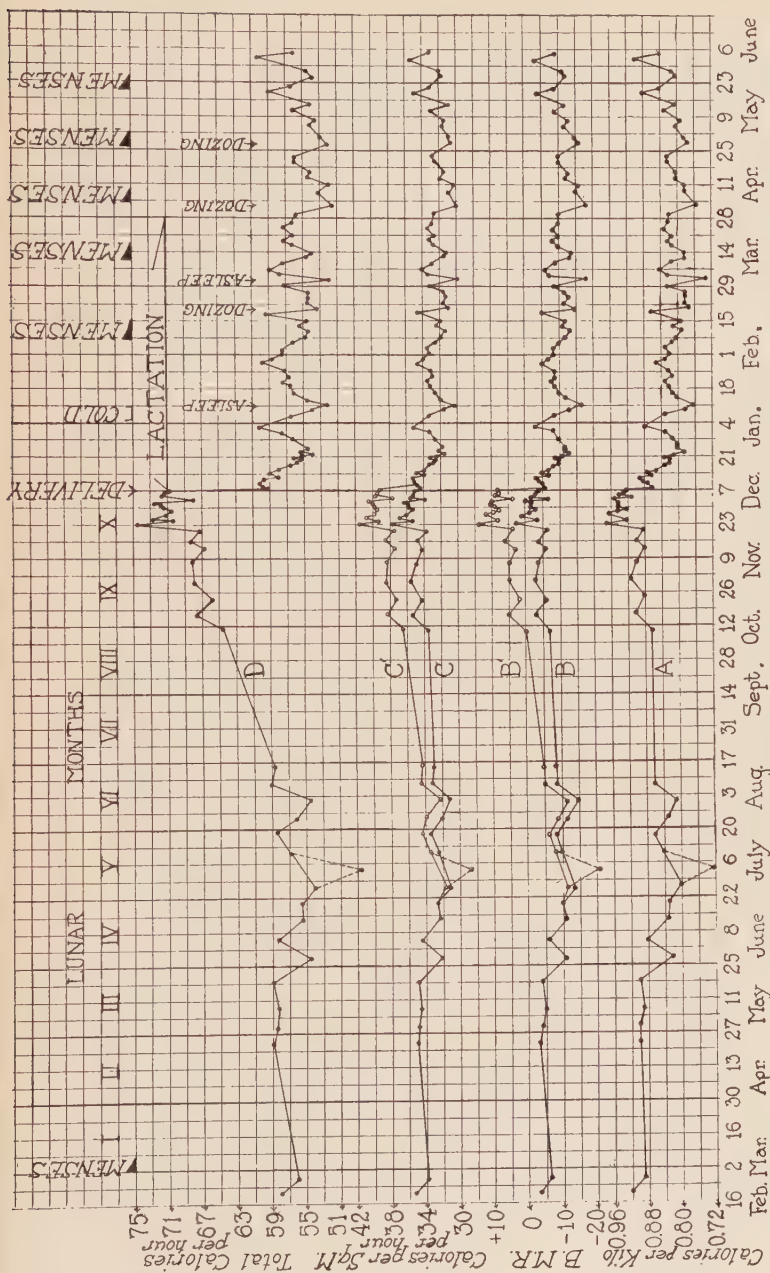


FIG. 79.—“Basal metabolism findings before, during, and after pregnancy. The subject, a woman, aged thirty-four years, height 160 cm. Curve A represents the calories for each kilo; Curve B, the basal metabolic rate calculated during the course of pregnancy, by dividing the total calories each hour by the sum of the surface area of the mother and fetus, and comparing the result obtained with the Du Bois normal of the mother, 36.5 calories. Curve B' represents the basal metabolic rate calculated in the usual method, using the Du Bois surface area and normal standards. Curve C is the calories for each square meter each hour derived for the course of pregnancy as just described for Curve B. Curve C' represents the calories for each square meter each hour, obtained by dividing the total calories each hour by the Du Bois surface area obtained by using the total weight of mother and fetus in the usual manner. Curve D represents the total calories for each hour.” (Sandiford and Wheeler.)

during pregnancy, the metabolism averaging 17 per cent early in gestation and mounting in a straight line to +7 per cent just before delivery. After the child was born there was a rapid drop to -10 per cent with a slight rise in the next few weeks. Sandiford and Wheeler¹ have recently published a classical study of a woman, para IV, whose metabolic rate was observed before conception, through a normal pregnancy and long after the cessation of lactation, a period of seventeen months. The results are shown in Fig. 79. The surface area of the fetus was estimated according to a method devised by Sandiford² and added to the surface of the mother. The sum of these two surface areas divided into the calories produced per hour gave almost a level line throughout pregnancy. Similar results were obtained when these authors recalculated other cases from the literature. They conclude that the energy production of a unit mass of the mother's protoplasmic tissue remains unchanged throughout the course of pregnancy, and that such increases in the total heat production as occur are due to the increasing mass of active protoplasmic tissue, consisting in large part of the fetal tissues and in lesser part of maternal structures. Sandiford and Wheeler encountered no increase in heat production during lactation but rather a decrease probably due to a less active life. Menstruation had no appreciable effect.

It is of considerable importance for us to be able to estimate the muscular effort and heart strain during child-birth. We are therefore grateful to Knipping and Theodor³ who made actual measurements of the oxygen consumption as the child passed through the pelvis. In one woman the heat production was 69 calories an hour before delivery and increased until it reached the rate of 121 calories per hour during the ten minutes of greatest effort. In another case it rose from 59 calories to 81 calories. Knipping and Theodor estimate that the labor of child-birth is equivalent to one-half hour of heavy bodily work or three hours of light work. This is very little when we consider the apparent distress and exertion. The work of the heart is evidently not unduly increased and this perhaps explains the surprising manner in which women with cardiac lesions pass successfully through the perils of child-birth.

¹ Sandiford and Wheeler: *Jour. Biol. Chem.*, 1924, **62**, 329.

² Sandiford: *Jour. Biol. Chem.*, 1924, **62**, 323.

³ Knipping and Theodor: *Zentralbl. f. Gynäk.*, 1922, **46**, 1082.

CHAPTER XV.

BASAL METABOLISM IN DISEASES OF THE BLOOD.

Primary and Secondary Anemias.—In discussing the basal metabolism of patients with a diminished amount of hemoglobin, we must remember that this is merely one of the manifestations of the malady. In secondary anemias, the metabolism may be influenced more or less profoundly by the lesion which causes the anemia. In the so-called primary pernicious anemia, the cause is unknown and for this reason we cannot estimate its effects on metabolism. In both forms of anemia there may also be secondary changes due to the diminished power of the blood to supply oxygen to the tissues. There is a tendency toward a fatty degeneration of the cells which leads to impaired function of all the organs. As a rule the patients are weak and are obliged to lead a sedentary life which in itself tends to lower the basal metabolism. This disability may be accentuated by lesions of the spinal cord in pernicious anemia. The picture is also complicated by periods of marked remission which occur spontaneously or as a result of treatment. These are usually accompanied by an outpouring of young blood cells which show active oxygen consumption in themselves.

Literature.—The literature of this subject has been well covered by Strauss,¹ Mohr,² Meyer and Du Bois,³ Murphy, Means and Aub,⁴ Tompkins, Brittingham and Drinker,⁵ and Grafe.⁶

We shall pass over a large amount of work which has been performed on animals following blood-letting, since the technic has usually been inadequate. The conflicting results point to comparatively slight changes in the metabolism.

¹ Strauss: *Metabolism and Practical Medicine* (von Noorden), Chicago, 1907, 2, 350.

² Mohr: *Oppenheimer's Handb. d. Biochem.*, Jena, 1910, 4, Part II, 372.

³ Meyer and Du Bois: *Clin. Cal.* 15, *Arch. Int. Med.*, 1916, 17, 965.

⁴ Murphy, Means and Aub: *Clin. Cal.* 23, *Arch. Int. Med.*, 1917, 19, 890.

⁵ Tompkins, Brittingham and Drinker: *Arch. Int. Med.*, 1919, 23, 441.

⁶ Grafe: *Ergeb. des Physiol.*, 1923, 21, Part II, 1.

The first clinical investigation was made by Pettenkofer and Voit¹ on a man with leukemia. Kraus and Chvostek² and Kraus³ made an extensive study of various forms of anemia, using the Zuntz-Geppert method. The patient sat in a chair and most of the observations came twelve to fifteen hours after the last meal, but in some cases tests were performed five hours after a breakfast of milk and coffee. At this early date the technic was not entirely satisfactory and it is not surprising that Kraus found a level of oxygen consumption in anemia which was higher than that of the modern investigators. Magnus-Levy⁴ whose technic seems always to have been faultless was unable to discover in primary and secondary anemias any marked departure in metabolism from the normal.

Thiele and Nehring⁵ observed comparatively slight changes in anemia, the recalculation of their results in chlorosis indicating that the metabolism was near the lower normal limits. Meyer and Du Bois⁶ studied a few patients with pernicious anemia in the respiration calorimeter and found that the methods of direct and indirect calorimetry agreed within 3.3 per cent. Such a divergence of the two methods is often found in short experiments with small groups of patients and does not seem to indicate any strikingly abnormal metabolic processes. In their 3 mild cases the basal metabolism showed a slight increase, in 2 severe cases, the demand for oxygen was from 7 to 33 per cent above the normal average, but 1 of these patients was somewhat restless during these experiments. The respiratory quotients were normal and the percentage of calories furnished by protein was about the same as in health. This was, of course, largely a reflection of the normal diet of the previous days. Tompkins, Brittingham and Drinker⁷ using a Tissot spirometer followed a number of patients with anemia during various forms of treatment. They found all the cases between -26 per cent and +20 per cent. The milder cases tended to show a normal metabolism. In general, the long-standing chronic cases gave a

¹ Pettenkofer and Voit: *Ztschr. f. Biol.*, 1869, **5**, 319.

² Kraus and Chvostek: *Wien. klin. Wchnschr.*, 1891, **4**, 605.

³ Kraus: *Ztschr. f. klin. Med.*, 1893, **22**, 457, 573.

⁴ Magnus-Levy: *Ztschr. f. klin. Med.*, 1906, **60**, 177.

⁵ Thiele and Nehring: *Ztschr. f. klin. Med.*, 1896, **30**, 41.

⁶ Meyer and Du Bois: *Clin. Cal.* **15**, *Arch. Int. Med.*, 1916, **17**, 965.

⁷ Tompkins, Brittingham and Drinker: *Arch. Int. Med.*, 1919, **23**, 441.

diminished and the recent more acute cases, an elevated metabolism, but in some patients, the high metabolism was in part due to fever. Transfusion caused a diminution in metabolism which lagged several days behind the improvement in blood and general condition. These authors believe that, in untreated acute cases, there is some type of stimulation to the body cells in general and that, in chronic cases and those that have been treated by transfusion, there are coincident progressive tissue alterations which tend to reduce metabolism. If we consult on pages 297 and 299 the tables which give the findings of Boothby and Sandiford¹ in diseases not connected with the thyroid gland we note that a total of 55 patients with secondary anemia were studied. Of these 1 showed a low metabolic rate, 6 had high rates and all the others were within normal limits. In their series of 55 patients with splenic or pernicious anemia 5 were low and 21 distinctly high. Grafe² ascribes the increase in metabolism to an increased activity of the blood-forming organs. He cites a patient with severe hemolytic anemia who was studied three times in the course of a year. During a blood crisis the metabolism rose from 1580 calories a day to 1639 and a year later with no change in body weight fell to 1389 with an increasing exhaustion of the bone-marrow.

In reviewing the results quoted above, it is difficult to be certain as to the factors in primary or secondary anemia which influence the basal metabolism. It is true, that some patients show a low metabolism, but we cannot rule out the effect of the muscular weakness and sedentary life. A few show distinctly abnormal elevations in metabolism, but this may be largely due to complications rather than the anemia *per se*. The best evidence pointing toward a specific elevation due to anemia is the fall in metabolism which Tompkins, Brittingham and Drinker demonstrated after transfusion. It is interesting to note that Kakehi³ has obtained indications of a decreased muscular efficiency in anemia.

Leukemias.—The basal metabolism in leukemia may be as high as in the severe types of Graves' disease. There seems to be no relationship between the pathological findings in these two diseases though the causative factors in both mal-

¹ Boothby and Sandiford: Jour. Biol. Chem., 1922, 54, 783.

² Grafe: Ergeb. der Physiol., 1923, 21, Part II, 1.

³ Kakehi: Biochem. Ztschr., 1916, 76, 248.

adies remain unknown. In the leukemia, the greatly increased proportion of white blood cells is a manifestation of profound change in the hemopoietic system. Since the causative factor is unknown we may be dealing with some toxic agent which of itself affects metabolism.

A review of the literature is complicated by the confusion in regard to the nomenclature of the various types of disease. Pettenkofer and Voit's patient was suffering from severe leukemia and, although they found his gaseous exchange almost the same as that of a healthy man on the same diet, Magnus-Levy calculated at a later date that an increase in metabolism was actually revealed. Kraus and Chvostek¹ and Kraus² and Bohland³ studied various leukemias. Kraus and Chvostek apparently did not recognize the abnormally high metabolism, in their patients, but Bohland established a definite increase. Magnus-Levy who found an increased basal metabolism in leukemia also studied the urinary constituents. It was Grafe,⁴ in 1911, who first gave us a clear picture of the extreme increase in basal metabolism, finding in leukemias a rise of 25 to 100 per cent above the average normal, the degree of increase being nearly parallel to the severity of the clinical picture. There seemed to be no qualitative change in the metabolism since the respiratory quotients were normal and the protein on an average furnished about 11.4 per cent of the total calories. Murphy, Means and Aub⁵ studied, in the Sage calorimeter, a man with lymphatic leukemia whose basal metabolism on admission was 44 per cent above the average normal. They followed his oxygen consumption during a period of treatment, first with roentgen-rays and then with radium. The metabolism fell slightly with rest in bed and the intensive treatment with roentgen-rays scarcely changed this level, although it caused a marked drop in leukocytes. Later treatment with radium again diminished the leukocytes and caused a slight fall in the metabolism which reached 36 per cent above the average normal. They found that this patient eliminated through skin and lungs some 53 grams of water an hour which was

¹ Kraus and Chvostek: *Wien. klin. Wchnschr.*, 1891, 4, 605; *Ztschr. f. klin. Med.*, 1893, 22, 573.

² Kraus: *Ztschr. f. klin. Med.*, 1893, 22, 457.

³ Bohland: *Berl. klin. Wchnschr.*, 1893, 30, 417.

⁴ Grafe: *Deutsch. Arch. f. klin. Med.*, 1911, 102, 406.

⁵ Murphy, Means and Aub: *Clin. Cal. 23, Arch. Int. Med.*, 1917, 19, 890.

about twice as much as the average for normal men. Part of this increase was, of course, due to the higher metabolism but there was also an increase in the percentage of heat lost through vaporization. The leukemic man dissipated 29.5 per cent of his calories in this manner, whereas, the normals averaged about 24 per cent. The respiratory quotient was low but within normal limits and the percentage of calories derived from protein was also normal. The direct and indirect calorimetry agreed within 0.5 per cent.

Boothby and Sandiford,¹ in 16 cases of lymphatic and myelogenous leukemia found all but 2 with a basal metabolism above 20 per cent.

Gunderson² has reported on 19 cases of myelogenous leukemia. The basal metabolism, according to the Sage standards, ranged between 6 and 80 per cent above the average normal. There was a general tendency for the highest metabolic rates to be associated with the highest leukocytosis and this was especially characteristic in the patients that had not recently received treatment with radium. There were some with high metabolism and low leukocyte count and some with moderately increased metabolism and very high counts. Gunderson believes that his results indicate that the increase in basal metabolism bears at least as close a relation to the number of immature white cells as it does to the total leukocyte count. McAlpin and Sanger³ in studying 16 patients with leukemia treated with roentgen-ray found that the basal metabolism and leukocyte count usually ran parallel courses but that sometimes a rising metabolic rate foretold an approaching increase in white blood cells.

One case of acute lymphatic leukemia is reported by Lennox and Means.⁴ The basal metabolism was 40 to 55 per cent above the normal average and it followed the leukocyte count and temperature in a general way as these were influenced by roentgen-ray treatment. The basal metabolism seemed to be a truer indicator of the severity of the process than the blood count.

The importance of the young blood cells as chief factors in causing an increase in metabolism was pointed out by Grafe,⁵

¹ Boothby and Sandiford: *Jour. Biol. Chem.*, 1922, **54**, 783.

² Gunderson: *Boston Med. and Surg. Jour.*, 1921, **185**, 785.

³ McAlpin and Sanger: *Am. Jour. Med. Sci.*, 1924, **167**, 29.

⁴ Lennox and Means: *Arch. Int. Med.*, 1923, **32**, 705.

⁵ Grafe: *Deutsch. Arch. f. klin. Med.*, 1911, **102**, 406; *Ergeb. der Physiol.*, 1923, **21**, Part II, 465.

in 1911. He demonstrated an increased oxygen consumption of the blood itself and calculated that this would raise the total metabolism 14 per cent. Greater increases are conceivable on account of the collection of young leukocytes in the organs of the body. He points out that we may not find a strict parallelism between metabolism and leukocytes or rather the unripe forms because the mere count of these in the peripheral blood is no sure indicator of their production within the body.

It is quite possible that there are other factors which contribute to the increased metabolism. At times there is an exceedingly high-protein metabolism¹ and in some cases the uric acid is greatly increased. We do not know whether or not the blood-forming organs themselves have some internal secretion which affects metabolism. There may possibly be some specific effect on the thyroid. In this connection a recent analysis of the pulse-rate in leukemia is of great interest. Minot and Means² have proved that the increase of heart-rate in the blood disease for a given increase in metabolic-rate is just the same as in exophthalmic goiter. A leukemic patient with a metabolic rate of +50 per cent has about the same pulse-rate as a Basedow patient with a basal metabolism of +50 per cent.

Grafe³ has reported on 7 cases of lympho-granulomatosis, finding a moderate increase in metabolism except in 1 case where the basal figures were 64 per cent above the normal. He used for his normal base line the average of the Harris and Benedict and the Sage standards. One patient with a true lymph-node sarcoma was 8.8 per cent above the normal, 1 diagnosed as Kundrat's lymphosarcoma was 24 per cent above. In 1 of the patients with lympho-granulomatosis the use of roentgen-ray caused a drop from +12.8 to +1 per cent together with a fall in leukocytes from 13,000 to 5,100 and a rise in hemoglobin from 70 to 80 per cent. Grafe believes that the rise in metabolism is caused by a toxic influence and that this is diminished by roentgen-ray.

Lauter and Jenke⁴ have been able to reduce the nitrogen excretion of 2 patients with chronic leukemia down to the

¹ Edsall: *Trans. Assn. Am. Phys.*, 1905, **20**, 279.

² Minot and Means: *Arch. Int. Med.*, 1924, **33**, 576.

³ Grafe: *Klin. Wchnschr.*, 1922, **1**, 62.

⁴ Lauter and Jenke: *Deutsch. Arch. f. klin. Med.*, 1925, **146**, 323.

normal figure of 2.5 to 2.8 grams a day. One patient with lymphogranuloma was at this same level before roentgen-ray but the excretion rose to 5 to 8 grams after irradiation.

Basal Metabolism in Polycythemia.—The rare disease of erythremia (polycythemia rubra vera) is accompanied by great increase in the number of red blood cells and hemoglobin. It is a disorder primarily of the red cell elements of the marrow. This subject has been well reviewed by Gaisböck,¹ Mosse,² and Minot and Buckman.³ The metabolism seems to be distinctly affected as will be seen from Table 72. The cause of the increase is not clear, possibly it is due to increased blood

TABLE 72.—BASAL METABOLISM IN POLYCYTHEMIA.

Author.	Subjects.	Red blood cells, millions.	Hemoglobin.	Basal metabolism.
Mosse ⁴ . .	23 cases from the older literature	3.3 to 5.1 cc O: per kg. and min.
Abbott ⁵ . .	Patient, 58 yrs.	8.4	110	+16 to +29 per cent.
Grafe ⁶ . .	P. S., man, 30 yrs.	8.0	..	+42 per cent.
	F. K., man, 47 yrs.	10.6	..	+34 per cent.
	T., man, 41 yrs.	7.5	..	+33 per cent.
Isaacs ⁷ . .	Patient, man, 62 yrs.	9-16	160-190	+31 to +39 per cent.
Minot and Buckman ⁸	4 cases	+10 to +35 per cent. Av. +21 per cent.

volume with increased work of the organs. Although the earlier investigators found an increase in only a small proportion of the cases, all the later work with better technic and controls indicates a rather uniform stimulation of the oxidative processes. It seems more probable that it is caused by the blood-forming organs or else the immature blood cells as in the leukemias and anemias. Isaacs has suggested that there is a relationship between the basal metabolic rate and the uric acid production due to the destruction of nuclear material.

¹ Gaisböck: *Ergeb. d. inn. Med. u. Kinderh.*, 1922, **21**, 204.

² Mosse: *Kraus-Brugsch, Spez. Path. u. Therap. inn. Krank.*, 1920, **8**, 821.

³ Minot and Buckman: *Am. Jour. Med. Sci.*, 1923, **166**, 469.

⁴ Mosse: *Path. u. Therap. inn. Erkr.*, 1920, **8**, 821.

⁵ Abbott: *Canadian Med. Assn. Jour.*, 1918, **8**, 491.

⁶ Grafe: *Ergeb. der Physiol.*, 1923, **21**, Part II, 462.

⁷ Isaacs: *Arch. Int. Med.*, 1924, **31**, 289.

⁸ Minot and Buckman: *Am. Jour. Med. Sci.*, 1923, **166**, 469.

CHAPTER XVI.

METABOLISM IN DISEASES OF THE HEART AND KIDNEYS.

METABOLISM IN CARDIAC DISEASE.

IN chronic cardiac disease the lesion would seem to have purely mechanical effects. It is difficult to imagine any important medical condition in which the metabolism was less involved. Indirectly, however, there are many secondary manifestations which might affect the heat production. The increased size and work of the heart and the dyspnea so frequently encountered would raise the heat production while the individual was at rest. It is conceivable also, that the impaired circulation might change the oxygen demand of the tissues and also the functional activity of the ductless glands. We must not forget that patients with severe cardiac lesions lead sedentary lives and might, therefore, be expected to show a lowered metabolism. Kraus¹ made some early studies of cardiac patients while at rest and while working on an ergograph, but some of his patients showed quotients so far below the normal limits that he adopted a theory of abnormal metabolism which has since been abandoned. Grafe,² in some early work, using an apparatus which he has since discarded, also found some impossibly low quotients. Peabody, Meyer and Du Bois³ studied cardiac patients as well as nephritics in the calorimeter. They found no abnormal quotients and no significant divergence in the methods of direct and indirect calorimetry. The cardiac patients who were severely ill showed an increased metabolism, some of them giving figures of +28, +41 and +49 per cent. All of these patients were dyspneic. The milder cases without dyspnea were within normal limits with the exception of one man who was restless in the calorimeter. Hamburger and

¹ Kraus: *Bibliotheca medica*, Abt. D¹., No. 3, Cassel, T. G., Fisher & Co., 1897.

² Grafe: *Deutsch. Arch. f. klin. Med.*, 1909, **95**, 543.

³ Peabody, Meyer and Du Bois: *Clin. Cal. 16, Arch. Int. Med.*, 1916, **17**, 980.

Lev¹ have obtained similar results in a series of 17 cardiac patients, finding the increase in metabolism proportional to the degree of decompensation.

Peabody, Wentworth and Barker² studied 24 patients with cardiac disease, many of them complicated by chronic nephritis. They divided the subjects into two groups depending upon the relationship of the vital capacity to the average normal. In Group I, the vital capacities were all over 60 per cent of the average normal and the patients were in comparatively good clinical condition, all of them being comfortable while at rest. The average metabolism of this group was 2.5 per cent above the normal, 1 man with aortic and mitral insufficiency with a heart well compensated was 19 per cent above. In Group II, the vital capacities ranged from 30 to 60 per cent of the normal. Most of them were severely affected and those whose vital capacities were lowest tended to be dyspneic even while at complete rest in bed. Their basal metabolism averaged 13 per cent above the normal, 6 out of 14 being above +20 per cent. The highest metabolism of +40 per cent was found in a man acutely decompensated. Twelve days later, when he regained compensation, metabolism was +9 per cent. His vital capacity had risen from 30 to 52 per cent and his minute volume had fallen from 11.6 to 5.65 liters. The respiration rate had also fallen from 30 to 16 per minute. Meakins, Dautrebande, and Fetter³ also obtained slight increases in the gaseous exchanges in some cases of mitral stenosis. Dieuaide⁴ noted a slight increase in metabolism during an attack of ventricular paroxysmal tachycardia. Lev and Hamburger⁵ who had the unusual opportunity of studying a man who could produce paroxysmal tachycardia at will found the metabolism -6 per cent with a pulse-rate of 67 and +5 per cent when the pulse had jumped to 187.

Boothby and Willius⁶ have made a comprehensive report of 217 cardiac patients examined at the Mayo Clinic. They found a rather slight tendency toward an elevated metabolism. It was difficult to secure complete relaxation on the

¹ Hamburger and Lev: *Jour. Am. Med. Assn.*, 1925, **84**, 587.

² Peabody, Wentworth and Barker: *Arch. Int. Med.*, 1917, **20**, 468.

³ Meakins, Dautrebande, and Fetter: *Heart*, 1923, **10**, 153.

⁴ Dieuaide: *Bull. Johns Hopkins Hosp.*, 1924, **35**, 229.

⁵ Lev and Hamburger: *Am. Heart Jour.*, 1925, **1**, 240.

⁶ Boothby and Willius: *Med. Clin. North America*, 1925, **8**, 1171.

part of the patients and the subjective sensation of distress and the nervousness caused by the face mask were factors which added to the increased metabolism due to the labor of respiration. In their hypertensive cases most of the findings were within normal limits but some with decompensation showed a moderate increase. Out of a series of 100 patients with cardiac neurosis only three had distinctly high metabolism, the large majority being within the normal limits on the first or subsequent tests. Curiously enough in arteriosclerotic disease and myocarditis there was no correlation between metabolism and the degree of decompensation.

In general, it seems that there is nothing in heart disease of itself that alters the metabolism but that the increased activity of the muscles of respiration causes an increased oxygen consumption. It is also possible that the increased work of the heart helps to raise the metabolism to a slight extent. In this connection, it is perhaps well to remind the reader that patients with cardiac and renal disease continue to metabolize normal amounts of food (or body) substances even though they may be on very low diets. In these conditions the beneficial results are more probably due to the restriction of the fluid intake and the rest given to the gastro-intestinal tract.

METABOLISM IN NEPHRITIS.

The literature on the subject of the basal metabolism in nephritis is not voluminous. Hannover¹ studied 1 patient with contracted kidney, finding about the same carbon production as in a normal control. Apparently there was no other work until 1916, when Peabody, Meyer and Du Bois² investigated 6 patients in the calorimeter. In some of these there were cardiac complications. They studied at the same time 10 patients with heart disease. In the whole group respiratory quotients were within normal limits and the methods direct and indirect calorimetry agreed within 2 per cent, the direct method being the lower. They found that patients with compensated cardiac lesions or with mild nephritis showed no increase in metabolism. The patients

¹ Hannover: *De quantitate relativa et absoluta acidi carbonici ab homine sano et ægroto exhalati*, Havniæ, 1845. See also Möller, *Ztschr. f. Biol.*, 1878, 14, 542.

² Peabody, Meyer and Du Bois: *Clin. Cal.* 16, *Arch. Int. Med.*, 1916, 17, 980.

with dyspnea showed a rise in metabolism as might be expected from the increased muscular work. Aub and Du Bois¹ continued the study of nephritis during the next year. It so happened that this time the method of direct calorimetry gave a total figure 2.5 per cent higher than the indirect. This almost neutralized the divergence in the opposite direction obtained the previous year and when the two series were combined the totals by the direct and indirect methods agreed within 0.7 per cent. This agreement is just as close as in the group of normal controls and it shows that the calorific value of one liter of oxygen is the same in nephritics and normals. The authors point out, however, that there may be a striking change in the intermediary metabolism without great change in the calorific value of oxygen. This is seen in the work on diabetes. All of the 10 patients studied by Aub and Du Bois suffered from a severe grade of nephritis and 5 were examined shortly before death. Four of the patients were markedly edematous and these showed a tendency toward diminished metabolism both according to weight and according to surface area. This might be expected in an organism diluted by a large mass of inert fluid. One man with marked edema was 27 per cent below the average normal nine days before he died. One girl, aged thirteen years, was 40 per cent below the average for her age. She had been on a restricted diet, however, for two months before the calorimeter observation and the authors suggest that this may reduce the metabolism even more in a child than in an adult.

Five patients suffering from nephritis of the chronic interstitial type without edema were studied. One with marked uremia, three days before his death was restless in the calorimeter and his oxygen consumption was 29 per cent above the average, but it is doubtful if the resting metabolism exceeded the normal limits. In a third patient with high metabolism hyperthyroidism was suspected. The other 2 patients studied were near the upper normal level of metabolism.

Acidosis did not seem to have much effect on the total metabolism since most of the patients in which it was present gave results within the normal limits. All the patients with dyspnea showed an increased heat production. No constant

¹ Aub and Du Bois: *Clin. Cal.* 22, *Arch. Int. Med.*, 1917, **19**, 865.

effect of blood-pressure on metabolism was noted and the authors were not able to demonstrate any direct effects of the nitrogenous products retained by damaged kidneys. Bowen and Boothby¹ have reported on a few cases of chronic nephritis, 1 man with edema showed a basal metabolism of -19 per cent, 2 without edema were -2 per cent and -5 per cent. Two cases with myxedema complicated by nephritis showed low metabolism. They improved under thyroxin treatment.

Boothby and Sandiford² have listed in their tables on pages 297 and 299, 207 cases called "renal." Eighty-eight per cent of these are within 15 per cent of the normal average. Of 265 cases of essential hypertension 79 to 89 per cent are between -15 and +15 per cent most of the others showing an increased metabolism.

Grafe³ has recently added 3 patients studied in the uremic stage of nephritis. All were within normal limits. One, studied six days before he died, was 3.8 per cent below the average normal. Another with a great retention of metabolites was 10 per cent above the average three days before he died. Grafe ascribes this increase to his severe anemia since his hemoglobin was only 30 per cent. Epstein and Lande⁴ have noted that the metabolism in nephrosis is 8 to 18 per cent below the standards and they state that they have obtained beneficial results from thyroid therapy. Linder, Hiller, and Van Slyke⁵ confirmed this lowering of basal metabolism in nephrosis. In addition they made some interesting studies of the blood sugar and respiratory quotient after glucose ingestion in various types of nephritis. There was nothing to indicate that the carbohydrate combustion was less rapid than normal and they were inclined to ascribe the delay in the fall of the blood sugar to some factor, such as retarded glycogen formation, other than failure to burn the sugar.

Maurer and Siebert⁶ studied 20 nephritic patients without edema or dyspnea. Four of the gravest cases showed a marked increase in basal metabolism. High figures were

¹ Bowen and Boothby: *Jour. Urol.*, 1917, **1**, 469.

² Boothby and Sandiford: *Jour. Biol. Chem.*, 1922, **45**, 783.

³ Grafe: *Ergeb. der Physiol.*, 1923, **21**, Part II, 470.

⁴ Epstein and Lande: *Arch. Int. Med.*, 1922, **30**, 563.

⁵ Linder, Hiller and Van Slyke: *Jour. Clin. Invest.*, 1925, **1**, 247.

⁶ Maurer and Siebert: *Ztschr. f. klin. Med.*, 1924, **101**, 47.

obtained in preëclamptic toxemia, eclampsia, and nephritic toxemia of pregnancy by Stander and Peckham.¹ They did not find that the basal metabolism determinations were of much help in differentiating between the various toxemias of late pregnancy.

All the work on nephritis indicates that kidney insufficiency leaves the total metabolism almost unchanged.

METABOLISM IN ARTHRITIS.

The term arthritis covers a large number of clinical conditions including such widely different diseases as chronic deforming arthritis and acute rheumatic fever. Pemberton and Tompkins² have reported briefly on the metabolism of 29 cases. Their subjects were all soldiers studied in United States Army General Hospital No. 9. Eighty per cent of the cases showed a metabolism within the normal limits, but 20 per cent were slightly below the normal, the lowest figure being -21 per cent. Cecil, Barr and Du Bois³ studied 3 patients with severe arthritis deformans and found that 2 of them gave figures of +7 per cent and 1 of -13 per cent. The man with the low metabolism showed many ankyloses and extreme atrophy of the muscles. All 3 of the patients, on being given a liberal diet very low in protein, excreted between 2.6 and 3.6 grams of nitrogen a day, figures which are well within the normal limits for the nitrogen minimum. The patients who were suffering from gonococcus arthritis, gout and mild rheumatic fever were within the normal limits. One patient with acute arthritis and fever showed an increased metabolism as might have been expected. Boothby and Sandiford's tables on pages 297 and 299 show that out of 134 patients with arthritis 92 per cent were within 15 per cent of the normal. In conclusion, it would seem that the change in basal metabolism is such as might be expected in a crippling disease where the patients are forced to lead sedentary lives or remain bedridden.

Wentworth and McClure⁴ have reported 4 cases of gout in which both the basal metabolism and respiratory quotients were normal.

¹ Stander and Peckham: *Bull. Johns Hopkins Hosp.*, 1926, 38, 227.

² Pemberton and Tompkins: *Arch. Int. Med.*, 1920, 25, 241.

³ Cecil, Barr and Du Bois: *Clin. Cal.* 31, *Arch. Int. Med.*, 1922, 29, 583.

⁴ Wentworth and McClure: *Arch. Int. Med.*, 1918, 21, 84.

CHAPTER XVII.

FEVER.

Comprehensive Reviews of Subject of Fever.—It is not within the scope of this book to consider different theories regarding the causation of fever and we can refer only incidentally to the various metabolic phenomena which are not directly concerned with the respiratory metabolism. There are many good reviews of these subjects. Kraus¹ discussed the whole subject of fever and infection in von Noorden's system of metabolism. MacCallum² covered the field two years later in a lecture before the Harvey Society. Tigerstedt³ in 1909 wrote a classical discussion of the physiology of heat. Isaac Ott⁴ has written a little book on fever with a summary of the literature. One of the most comprehensive discussions is that of P. F. Richter.⁵ Lusk⁶ has treated the subject concisely in his text-book and Barbour⁷ has reviewed 161 articles which deal with the heat regulating mechanism of the body. Du Bois⁸ has treated the metabolism in fever in *Endocrinology and Metabolism*, and many of the charts and tables in this book are taken from that source. The literature on experimental fever in animals is still in great confusion. One of the best discussions will be found in the monograph of Grafe.⁹ In this same book there is an excellent treatment of the subject of fever in man.

The Regulation of Body Temperature and Metabolism in Fever.—When fever is at its height the basal metabolism is increased.

¹ Kraus: von Noorden's Metabolism and Practical Medicine, 1907, vol. 2.

² MacCallum: Arch. Int. Med., 1908, 2, 569.

³ Tigerstedt: Nagel's Handb. der Physiol., 1909, 1, 557.

⁴ Ott: Fever, New York, Hoeber & Co., 1914.

⁵ Richter: Oppenheimer's Handb. der Biochem., 1910, 4, Part II, 104.

⁶ Lusk: The Science of Nutrition, third edition, New York and Philadelphia, W. B. Saunders Company, 1917.

⁷ Barbour: Physiol. Rev., 1921, 1, 295.

⁸ Du Bois: Endocrinology and Metabolism, New York, D. Appleton & Co., 1922, 4, 95.

⁹ Grafe: Ergeb. der Physiol., 1923, 21, Part II. Klin. Wchnschr., 1923, 2, 1005.

From a clinical and physiological point of view, the most important phase of the subject is the manner in which the body accomplishes this rise in temperature and metabolism. Space does not permit us to discuss the various theories concerning the cause of fever. We cannot, however, omit a discussion of the regulation of body temperature since this throws great light on basal metabolism and clinical calorimetry. The writer has found that it is a great help in teaching the importance of the clinical phenomena of fever if the subject is approached from the standpoint of physics and metabolism.

Liebermeister¹ in 1870 studied the carbon dioxide output of 2 patients during and after a malarial chill. He considered that the carbon dioxide expired indicated the heat production. We know that the CO₂ is not the most accurate index but a curve showing Liebermeister's results gives an excellent picture of the phenomena. He demonstrated that the chill was accompanied by a great increase in heat production and that after the chill the metabolism fell to a level not far above that observed before the paroxysm began.

After the chill, Liebermeister notes that the temperature continues to rise although the heat production suddenly drops nearly to its former level. He aptly compares this to the action of the sun on the temperature of the air on the earth's surface. The sun exerts its maximum heat at midday. After noon, although the heat of the sun becomes less intense, the temperature of the air continues to rise for a considerable period and remains high even when the sun is set. Liebermeister² brought forward the conception that temperature regulation in fever is merely adjusted at a higher level than normal.

The first observations of a patient with malaria made by the method of direct calorimetry were conducted in 1892 by Isaac Ott,³ of Philadelphia, who used rather a crude instrument. He noted during the chill a great increase in heat production with a considerable decrease in heat elimination and confirmed Liebermeister's finding that after a chill the heat production fell although the temperature still remained

¹ Liebermeister: *Deutsch. Arch. f. klin. Med.*, 1871, 8, 153.

² Liebermeister: *Handb. der Path. und Therap. des Fiebers*, Leipzig, F. C. W. Vogel, 1875.

³ Ott: *The Modern Antipyretics*, second edition, Easton, Pa., 1892; *Fever, Its Thermostaxis and Metabolism*, New York, Hoeber & Co., 1914.

high. During the drop in temperature there was a great increase in heat elimination and in the water vaporized from skin and lungs without marked change in the heat production. In 1902, the Russians, Likhatscheff and Avroroff,¹ studied malarial patients in the large Paschutin calorimeter with which they measured both the heat production by the direct method and the carbon dioxide output. Their results in general confirmed the findings of Liebermeister and Ott and they concluded that the rise in body temperature depended on an increased heat production.

A large amount of work on patients with various infections has been done with the smaller types of respiration apparatus. Such experiments give only the oxygen consumption and the carbon dioxide production during periods of ten or fifteen minutes. In 1891, Kraus,² found, in fever, an increased metabolism of about 20 per cent and believed that this could be explained by the increased respiratory movements and increased protein destruction. His respiratory quotients were all within the normal limits and he concluded that they depended on the body conditions and that there was no qualitative change of metabolism in fever. Following this, a number of articles were published in which many of the respiratory quotients were so low that the authors assumed profound changes in the laws of metabolism. We now believe that the abnormal quotients were due to technical errors. Svenson,³ in 1901, made some excellent contributions to the study of convalescence in typhoid fever and pneumonia. In the first week of convalescence in typhoid the metabolism fell sharply, sometimes reaching an extremely low level. During the next two or three weeks it rose and many of the patients gave respiratory quotients between 0.9 and 1.02 fourteen hours or more after the last meal. Work experiments indicated that a typhoid convalescent used more oxygen in a given task than did a normal individual. Convalescents from pneumonia did not show this and their changes in metabolism and quotients were not so marked as in typhoid fever. At the present time, we believe that the low metabolism of the first week of convalescence is due to the marked under-

¹ Likhatscheff and Avroroff: Report of Imperial Military Academy, St. Petersburg, 1902, vol. 5, Parts III and IV.

² Kraus: *Ztschr. f. klin. Med.*, 1891, 18, 160.

³ Svenson: *Ztschr. f. klin. Med.*, 1901, 43, 86.

nutrition during the long febrile attack and that the high quotients of the later weeks are due to the liberal amounts of carbohydrate food consumed by patients who have been almost starved. Schick and Cohen¹ have noted this same lowered metabolism in children after infectious diseases.

Löning² studied the specific dynamic action of food in fever and observed practically no increase after giving glucose. Sugar was rapidly oxidized and the quotient dropped to its original level within three or four hours after its administration. In 1911, Grafe,³ and also Rolly,⁴ using improved apparatus, studied patients with various infections. They both found quotients within normal limits, low during fever and high in convalescence. The oxygen consumption was 10 to 40 per cent above normal in fever, almost normal in early convalescence and rather high during the periods of liberal feeding in the latter part of convalescence.

The protein metabolism is usually greatly elevated in severe infections. The older writers believed that this was due to a toxic destruction of protein and that nitrogen equilibrium could never be attained. Von Leyden and Klemperer⁵ were unable to bring their fever patients into nitrogen equilibrium even though they gave extremely large amounts of protein in the diet. They did, however, diminish the body losses by giving protein or fat and carbohydrate. Shaffer and Coleman,⁶ working in Bellevue Hospital in New York, were the first to bring typhoid patients into nitrogen balance, but they had to use diets containing 3500 to 5200 calories per day. The chart of one of their patients is given below. It will be noticed that the nitrogen balance became strongly negative when the caloric intake was diminished and the carbohydrates reduced. Grafe⁷ pointed out that in his patients the protein furnished an average of 19.6 per cent of the total calories and maintained that the work of Shaffer and Coleman proved that there was no toxic destruction of protein. The argument that typhoid patients do not call

¹ Schick and Cohen: *Am. Jour. Dis. Child.*, 1925, **30**, 291. Schick, Cohen and Beck: *Ibid.*, 1926, **31**, 228.

² Löning: *Klin. Jahrb.*, 1908, **19**, 183.

³ Grafe: *Deutsch. Arch. f. klin. Med.*, 1911, **101**, 209.

⁴ Rolly: *Deutsch. Arch. f. klin. Med.*, 1911, **103**, 93.

⁵ Von Leyden and Klemperer: *Von Leyden's Handb.*, 1904, **2**, 322.

⁶ Shaffer and Coleman: *Arch. Int. Med.*, 1909, **4**, 538.

⁷ Grafe: *Deutsch. Arch. f. klin. Med.*, 1911, **101**, 209, and 1914, **116**, 328; *München. med. Wchnschr.*, 1913, **60**, 569.

upon protein to furnish a greater percentage of the calories is not convincing. Normal men often derive 20 per cent of their calories from protein fourteen hours after the last food but this is a mere reflexion of an unnecessarily liberal supply of protein in their previous diet. Shaffer and Coleman¹ really proved that it was necessary to give the patient about twice as many calories as he produced before he could be brought into nitrogen balance. They showed that typhoid patients

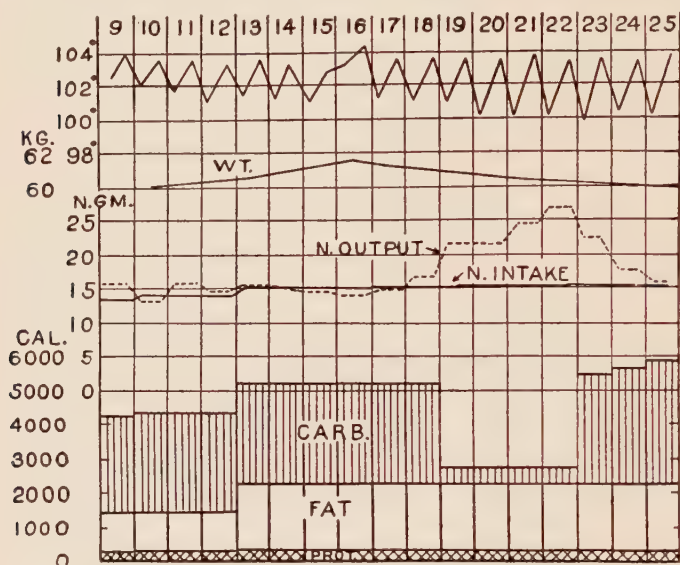


FIG. 80.—Typhoid patient, Z. O., studied by Shaffer and Coleman. He was maintained in nitrogen equilibrium by giving 5000 calories per day. The line of dashes represents the urinary nitrogen plus 15 per cent of the food nitrogen, which is a liberal estimate for the amount excreted in the feces.

could not be reduced to the nitrogen minimum of normal individuals even though they were given an amount of food which would more than cover the caloric requirement

Kocher² demonstrated in Friedrich Müller's Clinic that the nitrogen minimum in fever was at a much higher level than in health and proved that this was not due to the increased heat production by means of the following simple experiment. He established himself and one of his associates at a constant minimal nitrogen excretion of about 3 grams by means of

¹ Shaffer and Coleman: *Arch. Int. Med.*, 1909, 4, 538.

² Kocher: *Deutsch. Arch. f. klin. Med.*, 1914, 115, 82.

diet which contained about 5000 calories and 1 gram of nitrogen. The heat production on one day was increased by a walk of 60 kilometers and the nitrogen excretion only rose about 2 grams. On this day the protein probably furnished only 2 per cent of the total calories. The fever patients on similar diets never excreted less than 10 grams of nitrogen in the urine until the temperature had fallen to normal. The chart of one of Kocher's patients is given below.

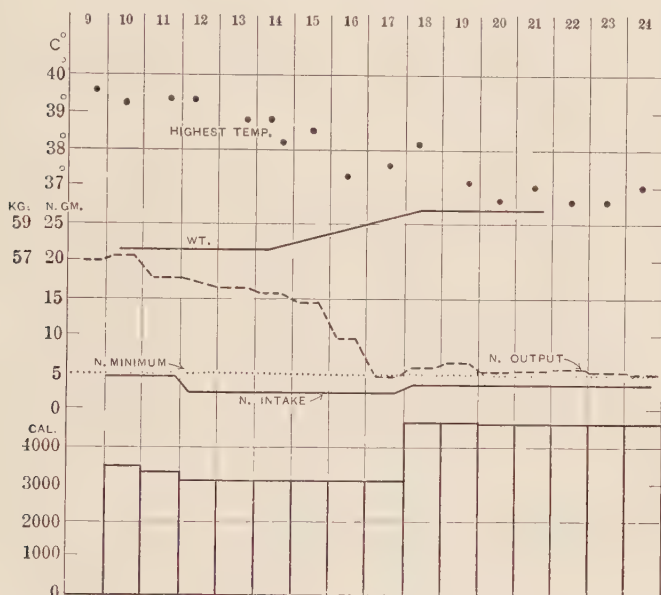


FIG. 81.—Nitrogen minimum experiment of R. A. Kocher on a patient with paratyphoid fever. The subject was given a liberal diet with low-nitrogen content but the nitrogen elimination did not approach the normal minimum until the temperature had fallen.

The study of the metabolism in typhoid fever was continued in Bellevue Hospital by Du Bois¹ and Coleman and Gephart² who showed that the large amounts of food given by Shaffer and Coleman to typhoid patients were absorbed practically as well as in health. The respiratory exchanges were studied by Coleman and Du Bois,³ first by means of the

¹ Du Bois: Arch. Int. Med., 1912, 10, 177.

² Coleman and Gephart: Clin. Cal. 6, Arch. Int. Med., 1915, 15, 882.

³ Coleman and Du Bois: Arch. Int. Med., 1914, 14, 168. For a graphic representation of their work consult Figs. 17 and 18 (pages 101 and 102) in Lectures on Nutrition, Mayo Foundation Lectures, 1924-1925, W. B. Saunders Company, Philadelphia and London, 1925, 77.

Benedict Universal respiration apparatus and later¹ in the respiration calorimeter of the Russell Sage Institute of Pathology. In their earlier work they confirmed the previous observations of Kraus, Svenson, Rolly and Grafe and found that metabolism at the height of the fever was 36 to 40 per cent above that of normal individuals. They showed that the liberal Shaffer-Coleman diet caused no appreciable increase in the heat production and that the reparative processes with high respiratory quotients could begin even during the latter part of the febrile period. They demonstrated that in order to bring the patient into nitrogen and weight equilibrium during the height of his fever it was necessary to give a diet which exceeded in calories the theoretical requirement by 50 to 110 per cent. They found no abnormal quotients and their work with the calorimeter confirmed the earlier investigations with the smaller apparatus and showed that the specific dynamic action of protein and carbohydrate is much smaller in the febrile period of typhoid than in health and in some cases seems to be absent. This is probably due to the fact that the protein metabolism is already very high and is not increased even by large amounts of protein in a given meal. The rise which would be expected after carbohydrate is probably masked by a diminution in protein metabolism. They also demonstrated that typhoid patients can store body fat on an abundant diet while losing body weight and body protein. Their findings concerning the mechanism of the rise and fall of body temperature will be discussed later. The evidence regarding the negative nitrogen balance in patients

TABLE 73.—SPECIFIC DYNAMIC ACTION OF PROTEIN AND CARBOHYDRATE IN HEALTH, FEVER AND CONVALESCENCE.

Subjects.	Number of experiments.	Average gm. of nitrogen or glucose in food.	Average gm. food per kg. body weight nitrogen or glucose.	Average per cent rise in metabolism.
Protein meal:				
Two normal men . . .	2	10.1	0.147	9.3
Four febrile patients . . .	6	8.6	0.174	4.5
Four convalescents . . .	5	10.2	0.217	16.6
Commercial glucose:				
Three normal men . . .	3	115.0	1.6	9.1
Two febrile patients . . .	4	115.0	2.2	1.0
Three convalescents . . .	3	115.0	2.7	9.8

¹ Coleman and Du Bois: Clin. Cal. 7, Arch. Int. Med., 1915, 15, 887.

receiving food calories in excess of their calculated heat production is shown in Table 74. Table 75 shows the amount of food required to bring typhoid patients into nitrogen equilibrium.

TABLE 74.—CHART SHOWING NEGATIVE NITROGEN BALANCES IN TYPHOID PATIENTS WHO RECEIVED FOOD CALORIES IN EXCESS OF CALCULATED HEAT PRODUCTION.

Patient.	Dates or days of disease inclusive.	Days in period.	Range of maximum temperature, degrees F.	Calculated heat production, calories. ¹	Food, calories. ¹	Food, N, gm. ¹	Nitrogen balance, gm. ¹
M. S. . .	Oct. 23— Nov. 3	12	102.8–104.6	2266	2863	16.4	–4.4
	Dec. 19–24	6	101.9–105.1	2085	2989	13.2	–2.4
C. F. . .	Nov. 28–30	3	101.2–103.4	1752	2458	12.0	–4.6
K. S. . .	Jan. 12–18	7	101.0–105.0	2197	2985	16.1	–3.2
	Jan. 19–22	4	98.8–99.0	1678	2819	14.6	–1.9
J. K. . .	Dec. 15–20	6	103.2–104.0	2568	3322	15.0	–7.4
	Days of disease						
F. W. ² . .	11–14	4	104.0–105.4	2200	2250	11.3	–5.0
	15–19	5	103.0–104.0	2238	3320	15.3	–3.3
	20–23	4	101.0–103.6	2054	2362	15.9	–1.5

¹ Figures given are averages for twenty-four hours.

² Taken from Coleman and Du Bois, 1914.

TABLE 75.—FOOD REQUIRED TO BRING TYPHOID PATIENTS INTO NITROGEN EQUILIBRIUM.

Name.	Day of disease.	Range of max. temp.	Average food cal. per kg. per 24 hrs.	Average food N. per 24 hrs.	Average N. balance per 24 hrs.
R. N. ¹ . . .	20–24	104.4–102.0	71.	10.9	+1.5
U. H. ¹ . . .	27–30	100.4–101.0	68.	8.9	+0.4
Z. O. ¹ . . .	9–12	104.0–103.2	72.	13.9	–0.2
Z. O. ¹ . . .	13–18	103.6–102.8	85.	15.0	+0.6
C. N. ² . . .	28–31	102.0–101.8	69.	18.7	+6.0
M. K. ² . . .	15–17	102.0–100.5	79.	17.9	+1.5
P. R. ² . . .	14–15	102.0–102.0	67.	17.6	+2.7
J. N. ³ . . .	26–30	102.0–104.0	58.	17.8	+1.9
F. W. ³ . . .	24–28	101.0–99.6	74.	20.3	+4.9
F. M. ⁴ . . .	6–8	103.1–103.6	45.5	10.5	–0.5
J. G. ⁵ . . .	9–10	103.6–103.8	59.5	7.5	+0.4
J. G. ⁵ . . .	16–21	100.9–103.4	76.6	8.1	+0.03

¹ Shaffer and Coleman.

² Du Bois.

³ Coleman and Du Bois.

⁴ Rolland: Deutsch. Arch. f. klin. Med., 1912, 107, 440

⁵ Rolland: Boy, aged ten; weight, 26 kg.

The series of papers published from Bellevue Hospital removes all the theoretical objections to the Shaffer-Coleman high-calory diet. For clinical accounts of the improvement

in general condition, lowered mortality and increased rapidity of convalescence caused by this diet, the reader is referred to the original articles by Coleman.¹ Typhoid patients seem to get along exceedingly well on diets containing about 2500 calories with 12 to 15 grams of nitrogen. Larger amounts than this apparently do no harm but they are difficult to administer to most patients on account of their poor appetites.

The study of the basal metabolism in fever and the mechanism of heat regulation has been continued by the Russell Sage Institute of Pathology in Bellevue Hospital. Barr and Du Bois² studied the rise and fall of temperature in malarial fever and worked out a method for determining the difference between the curves of a rectal temperature and the average body temperature. McCann and Barr³ studied tuberculosis and found that the basal metabolism was usually within normal limits and that the increase caused by fever was not as large as in typhoid or malaria. Protein manifested about the same dynamic action as in normal men. The toxic destruction of protein was not marked and a minimal nitrogen excretion of 5 or 6 grams a day was established in several cases. They pointed out the dangers of forced feeding. The study of food requirements in tuberculosis was continued by McCann⁴ who studied the effects of various diets on typhoid patients and demonstrated that excessive amounts of carbohydrate or protein caused a considerable increase in respiration. Du Bois⁵ compared the level of basal metabolism in various fevers and found that it was rather closely proportional to the level of the body temperature. He suggested that this was an expression of van't Hoff's law. This will be discussed later. Cecil, Barr and Du Bois⁶ studied a few patients with rheumatism and investigated the chill and fever which follows a few minutes after the intravenous injection of proteose or typhoid vaccine. The metabolic phenomena of this paroxysm proved to be almost exactly the same as those found in malaria. All of these papers from the

¹ Coleman: Jour. Am. Med. Assn., 1909, **53**, 1145, and 1912, **59**, 363; Am. Jour. Med. Sci., 1912, **144**, 659.

² Barr and Du Bois: Clin. Cal. 28, Arch. Int. Med., 1918, **21**, 627.

³ McCann and Barr: Clin. Cal. 29, Arch. Int. Med., 1920, **26**, 663.

⁴ McCann: Arch. Int. Med., 1922, **29**, 33; Am. Rev. Tuber., 1922, **5**, 870.

⁵ Du Bois: Jour. Am. Med. Assn., 1921, **77**, 352.

⁶ Cecil, Barr and Du Bois: Clin. Cal. 31, Arch. Int. Med., 1922, **29**, 583; Barr, Cecil and Du Bois: Clin. Cal. 32, Arch. Int. Med., 1922, **29**, 608.

Russell Sage Institute of Pathology dealt with the regulation of body temperature and the findings will be discussed later.

Grafe¹ has made an exceedingly interesting study of the metabolism of 10 patients with active, open, very severe but afebrile tuberculosis. Three showed little or no rise in basal metabolism but all the others were from 20 to 36 per cent above the average normal. Grafe could find no satisfactory explanation for this increase. McCann² ascribes the high figures in these very ill patients to the long experimental period in the Jaquet respiration chamber. He points out the fact that it would require almost superhuman efforts to remain motionless four to seven hours. The nitrogen metabolism was low and the rise in pulse and respiration not sufficiently marked to cause much increase in heat production. Three patients with a very severe grade of tuberculosis and temperature over 39° C. showed a marked increase in metabolism (+50 to +75 per cent).

Balcar, Sansum and Woodyatt³ have made some striking experiments on dogs producing an extremely high body temperature of 125.6° F. when they depleted the water reserves of the body by means of glucose injections which caused a marked diuresis. It has long been known that the inanition fever of new-born babies is due to dehydration. Bakwin⁴ has demonstrated the abnormally high concentration of serum protein in their blood and has shown that the administration of water will bring both temperature and concentration to normal level in a few hours. Barbour⁵ and his associates have shown that in dogs there are marked changes in the dilution of the blood when the animals are placed in hot or cold baths. Just what relationship the water mobilization has to the fevers of man is not yet clear.

The Temperature Regulating Mechanism in Fever.—Leaving aside all theories we have to face certain facts. In health man's body temperature is extraordinarily uniform, falling slightly below 37° C. in the early morning, rising slightly above it in the afternoon. Exceedingly few normal

¹ Grafe: München. med. Wchnschr., 1920, 67, 1081.

² McCann: Calorimetry in Medicine, Williams & Wilkins Company, Baltimore, 1924. (Also in Medicine, 1924, 3, 1.)

³ Balcar, Sansum and Woodyatt: Arch. Int. Med., 1919, 24, 116.

⁴ Bakwin: Am. Jour. Dis. Child., 1922, 24, 497, 508.

⁵ Barbour *et al.*: Am. Jour. Physiol., 1924, 67, 366, 378, 388, 399, 1924, 69, 654.

individuals show any appreciable deviation from the normal range. Violent exercise or extremes of environmental temperature cause transient deviations which are quickly rectified when normal conditions again prevail. In most fevers the body temperature shows sudden elevations and depressions. In certain infections such as pneumonia and typhoid fever, in its second week, the body is maintained at an elevated

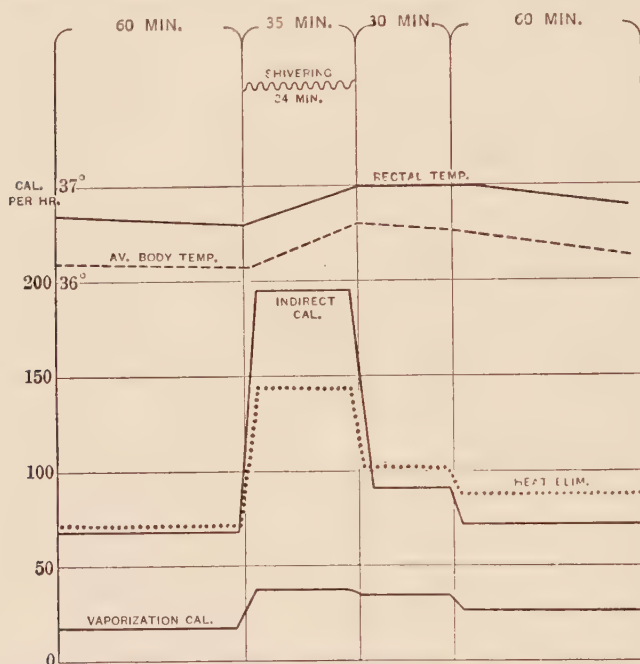


FIG. 82.—Calorimeter experiment on a normal man, shivering in imitation of a malarial chill. After a period of sixty minutes he shivered violently for thirty-five minutes, and then remained quiet. The heat production rose sharply, the temperature scarcely rose at all. The dotted line shows heat elimination, the continued line heat production by the method of indirect calorimetry.

temperature with fluctuations that are scarcely greater than those found in health. The temperature regulating mechanism of the body apparently maintains this higher level as jealously as it maintains the lower level of normal individuals.

Malarial Chills.—The mechanism of a sudden rise and fall in temperature is best studied in malarial fever and the malarial-like paroxysm caused by the intravenous injection of foreign protein. We have referred to certain experiments on these conditions made in the respiration calorimeter of

the Russell Sage Institute of Pathology. In order to demonstrate more clearly the effect of the pathological processes the writer copied a malarial chill while in the calorimeter.¹ During the first period of one hour he lay motionless in order that the level of the basal metabolism might be established. Then for thirty-five minutes he reproduced as closely as possible the shivering movements of one of the malarial

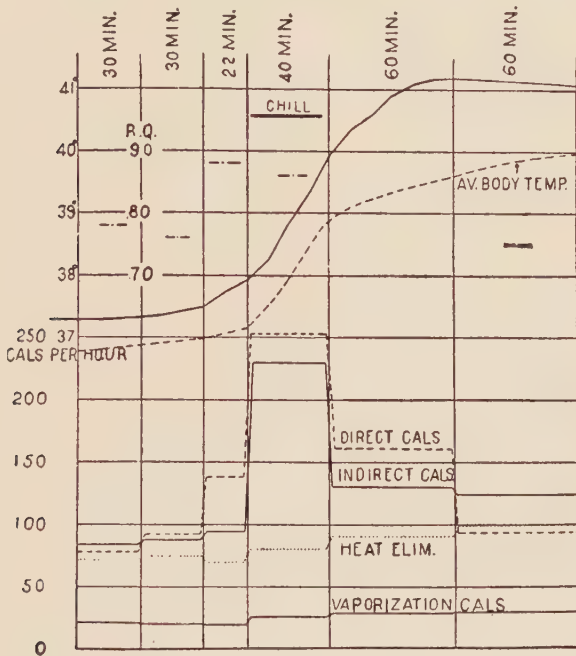


FIG. 83.—Malarial patient, George S., metabolism during chill.

patients who had been previously studied. This exercise which was no greater than that of the malarial patient, proved to be distinctly fatiguing. A large amount of extra heat was produced and in sharp contradistinction to the malarial case, was eliminated from the body surface almost as rapidly as it was formed. The rise in body temperature amounted to only 0.5°C . In the period after the chill there was a slight lag in elimination of some extra heat and there was a moderate increase in the vaporization of water. Within

¹ Hitherto unpublished. Consult Richardson and Levine: Clinical Calorimetry 39, Jour. Biol. Chem., 1925, 66, 161.

ninety minutes of the end of the chill conditions had returned to normal.

Let us now consider the results obtained in the malarial patient George S. whose chill had been imitated by the normal man. During the first sixty minutes the patient was in the calorimeter, his temperature was normal and practically all the heat which he produced within his body was eliminated by the usual mechanism of radiation, conduction, and the vaporization of water from skin and lungs. In the third

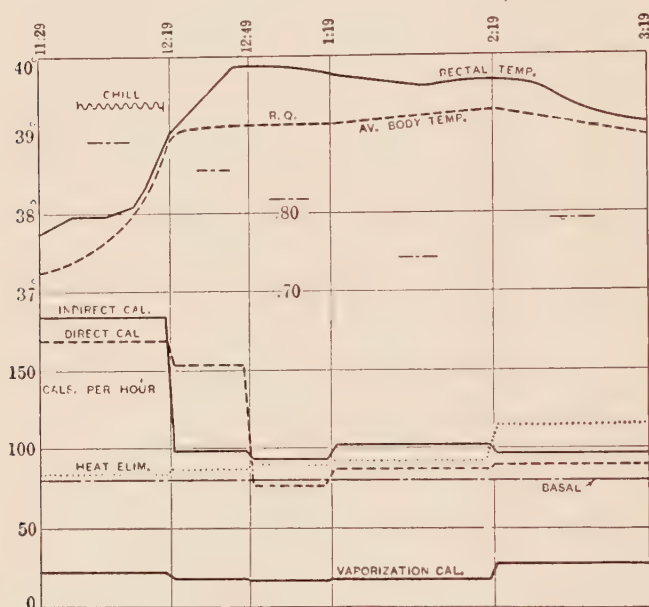


FIG. 84.—Effect of intravenous injection of foreign protein.

period there were indications of a rise in body temperature and by quick manipulation of the calorimeter the fourth period was started just before the patient began to shiver and shake. The chill lasted thirty-four minutes and the experimental period was ended five minutes after the patient had become quiet. Although his heat production had increased approximately 200 per cent, there was no change in his heat elimination. This, of course, proved that all the extra heat had been stored in the man's body and indeed the rectal temperature in this forty-minute period rose 2° C. In the fifth period of sixty minutes the patient was quiet, but his heat

production was 80 per cent above the normal basal level. The rectal temperature continued to rise sharply because the heat elimination was only slightly increased and was still far below the heat production. In the next period of sixty minutes the heat production was lower and was almost equalled by the rising heat elimination. In these two periods after the chill the vaporization of water from the skin and lungs was not only above the normal in actual grams, but it also bore a larger share than normal of the total heat elimination. This particular experiment was stopped two hours after the chill. Experiments which were performed on other patients during the fall of temperature after the chill showed an increased heat elimination which was far greater than the heat production. Almost exactly the same phenomena were observed in the experiments following the intravenous injection of typhoid vaccine.¹

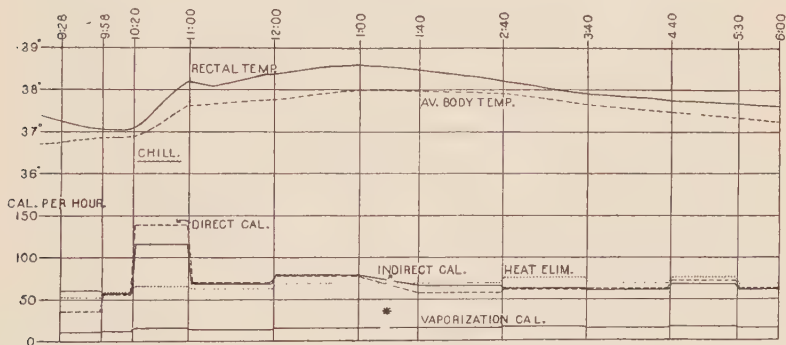


FIG. 85.—Effect of intravenous injection of typhoid bacilli.

The Human Body as a Physical Mass.—It is necessary at this point to consider some questions regarding the physics of the body. In health, if the body is to remain at constant temperature, all the heat produced is promptly eliminated. This is accomplished chiefly by two avenues of heat loss: (1) Radiation and conduction of heat to the surrounding air and, (2) the vaporization of water eliminated from the skin and lungs. Every gram of water which is vaporized at 23°C . absorbs 0.584 calories. Under ordinary conditions the heat lost in the vaporization of water constitutes about 24 per cent of the total heat eliminated.

¹ Barr, Cecil and Du Bois: Clin. Cal. 32, Arch. Int. Med., 1922, 29, 608.

To raise 1 kilogram of water 1° C. requires 1 calory. The human body has a lower specific heat than water and is said to average 0.83, and this figure, probably somewhat inaccurate is the one usually accepted. This means that when 1 kilogram of body tissue is raised 1° C. it requires 0.83 calories. If, therefore, the temperature of a man weighing 70 kilograms should rise 1° C. within an hour, 70 times 0.83 calories or 58.1 calories would necessarily be stored in that man's body. During a rising temperature, therefore, the body acts as a reservoir in which extra heat is stored. During a falling temperature this surplus is released.

The Rectal Temperature and Average Body Temperature.— It is usually assumed by the clinician that the rectal temperature gives the best indication of the fluctuations in body temperature. In over 500 experiments in the Sage calorimeter the temperature has been read every four minutes by means of a rapidly recording, extremely accurate electrical thermometer which is inserted about 10 cm. into the rectal cavity. There have been many indications that this does not show with absolute accuracy the average changes in body temperature during periods of fluctuation. This can be readily understood since the rectum is only one spot in the body and is situated a long distance from the extremities. It gives us an accurate idea of the changes in deep temperature, but not the surface temperature. We must remember that in a man who weighs 70 kilograms about 15 kilograms is within 1 cm. of the surface. We might obtain an accurate idea of the average body temperature change if we used a number of thermometers on the surface, in the axillæ, mouth, etc., but it is almost impossible to make such readings during a calorimeter experiment. It is, however, not difficult to measure the skin temperature in an open room and the technic has been greatly improved by Benedict.¹ Working with Miles and Miss Johnson² he found that the skin temperature of a nude artists model in a cold atmosphere ranged between 20° and 30° C. When clothed the figures were between 28° and 34.7° C. Dr. and Mrs. Benedict and E. F. Du Bois³ have made observations of the skin temperature of

¹ Benedict: Asher-Spiro's *Ergeb. d. Physiol. Supp. Bd.* (Festschr. f. L. Asher), 1925.

² Benedict, Miles and Johnson: *Proc. Nat. Acad. Sci.*, 1919, 5, 218.

³ Benedict, Cornelia G., Benedict, F. G. and Du Bois, E. F.: *Am. Jour. Physiol.*, 1925, 73, 429.

men and women in a large bag through which was driven a current of very hot, dry air. Under these conditions the skin gave readings which were practically the same as those obtained in the rectum or vagina.

Barr¹ has devised a method which can be applied to calorimeter experiments. Repeated alcohol checks have shown that a good Atwater-Rosa-Benedict calorimeter measures with great accuracy the total heat elimination by the direct method and the total heat production by the indirect method. If, for instance, during a certain experimental period, the heat production is 100 calories and the elimination 60, this means the storage of 40 calories in the body. If the subject weighs 70 kilograms his hydrothermal equivalent is 58.1 liters of

water. $\frac{-40}{58.1}$ gives 0.69 the degrees C. that the average body temperature must rise during the experiment. If the heat production is less than the elimination the fall in temperature can be calculated in a similar manner. By making such computations for each experimental period the curve may be constructed which gives the direction and extent of the changes in temperature of the body mass as a whole. It never tells us the exact temperature at any one time but for purposes of calculation we assume that the curve starts 0.5° below the reading for the rectal temperature. In experiments on normal subjects the curves for the rectal and average body temperature are usually parallel and, indeed, this is true even in most fever patients. During sudden fluctuations of temperature, however, the two curves may have different slopes and occasionally they diverge in direction. This is shown in the diagrams of the experiments given in the previous pages and in Fig. 86.

As we have said before, the curve of the rectal temperature is usually parallel to the curve of average body temperature where there are no sudden fluctuations. For this reason, the method of direct calorimetry estimates the total heat production by assuming that the rectal temperature indicates the actual rise or fall of average body temperature. This temperature change in degrees C. is multiplied by the weight of the body and specific heat of 0.83 to find the heat stored in or lost from the body. The product is added to, or subtracted from, the heat eliminated from the body, giving the

¹ Barr and Du Bois: Clin. Cal. 28, Arch. Int. Med., 1918, 21, 627.

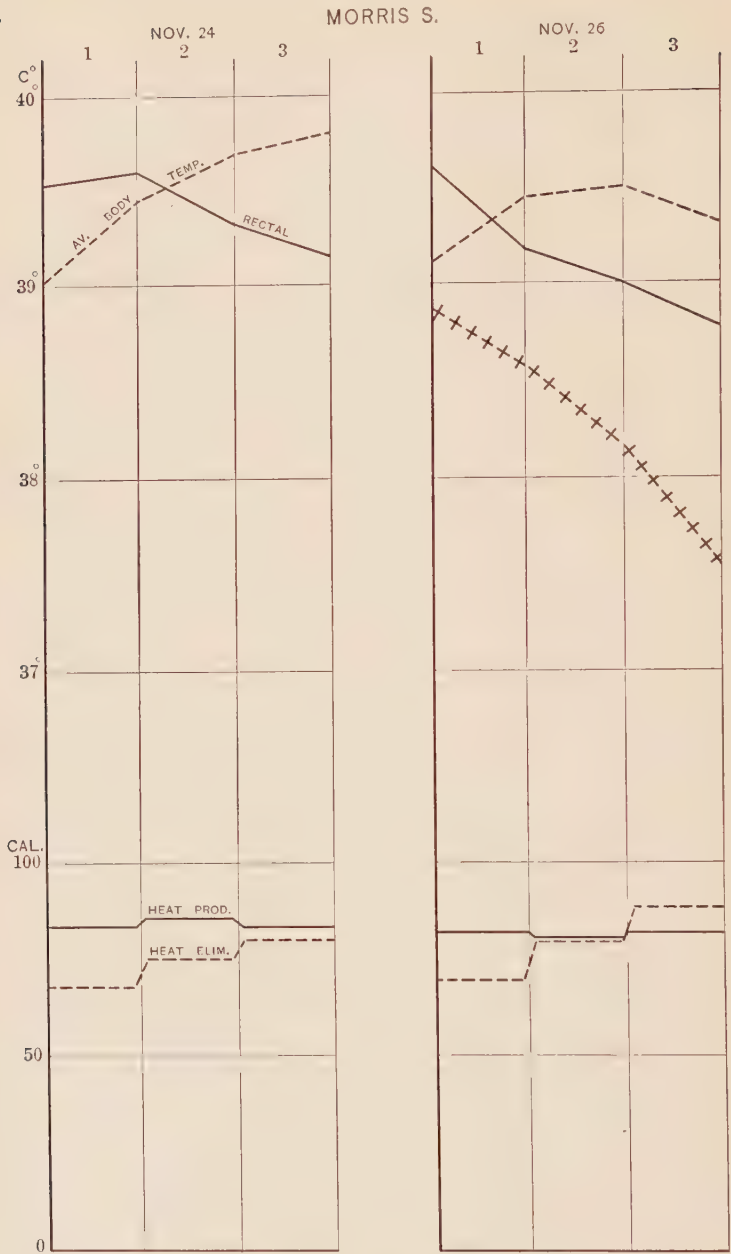


FIG. 86.—Typhoid patient showing differences in the change in the rectal temperature and the average body temperature. Crosses show surface temperature. (From Du Bois, *Endocrinology and Metabolism*, D. Appleton & Co., New York.)

total heat production by the direct method. In normal individuals and most afebrile patients it checks closely with the total heat production as calculated by the indirect method. In febrile patients, if this method of direct calorimetry is used the divergences are greater and, in typhoid fever the totals differed by 2.2 per cent, in tuberculosis by 5 per cent. In malarial fever, some of the observations were made with a rising temperature and some with a falling temperature, and it happened that the totals for the series agreed almost exactly, but in some of the short periods the two methods differed by as much as 22 to 25 per cent. In typhoid, Coleman and Du Bois¹ used two surface thermometers over thorax and abdomen. These were covered with pads of cotton so that they did not measure the actual skin temperature as influenced by evaporation, but gave readings which probably approximated those of the subcutaneous tissue. These surface thermometers indicated the changes in the average body temperature slightly better than the rectal thermometer but their readings were uncertain on account of the difficulty of keeping them in close contact with the skin.

Sudden Changes in Body Temperature.—Let us review the mechanism of the sudden rise and fall in body temperature. If we accept Liebermeister's theory, the heat regulating mechanism is suddenly established at a higher level than normal. The body finds itself relatively cold and, therefore, strives to produce extra heat which may be stored in the tissues. The only method of doing this rapidly is by means of physical exercise and some involuntary mechanism causes the patient to shiver until he has produced a large number of extra calories. Under ordinary conditions of health, these extra calories would be eliminated through the skin, but some coöperative mechanism prevents this during a chill. There is a constriction of the peripheral bloodvessels and the amount of heat carried to the surface is relatively small in proportion to the heat produced although the total amount is not greatly changed. The skin becomes colder than normal but apparently eliminates the same number of calories. The patient really changes his integument into a suit of clothes and withdraws the zone where the blood is cooled from the skin to a level some distance below the surface. Hamilton and

¹ Coleman and Du Bois: Clin. Cal. 7, Arch. Int. Med., 1915, 15, 887.

Barbour¹ have found under similar conditions a migration of water from the blood into the skin and subcutaneous tissues, thus padding the "suit of clothes." It would be more economical physiologically if the body could diminish actually as well as relatively the heat eliminated from the surface. Perhaps this is accomplished if we surround the shivering patient with hot-water bottles. There are indications in the calorimeter experiments that the rectal temperature rises more sharply than the average body temperature. This is to be expected, since the former represents the deep organs and the latter averages the deep organs and the extremities which are cold during the chill and warm up slowly.

After the temperature has established itself at its high level, the basal metabolism is increased and heat elimination and heat production are brought into equilibrium. Apparently a high level of metabolism is established, mainly as a result of the high temperature, possibly the high-protein metabolism and the toxins of the disease tend to increase the heat production also. The heat elimination is so adjusted that it equals the production and the skin is warmer than usual because it radiates more heat.

The fall of temperature takes place when the heat-regulating mechanism is shifted to a lower level. The body finds itself too warm and increases the heat elimination until it exceeds the production. The most rapid means of doing this is an outbreak of sweat, but in malarial fever and the fever after the intravenous injection of foreign proteins this does not seem to be sufficient to cool the body quite as rapidly as it was warmed by the more dramatic chill. The curves for the rectal temperature and average body temperature are nearly parallel because there is an increased circulation in the periphery which becomes almost as warm as the internal organs. There is also a gradual decrease in heat production on account of the steadily falling temperature. During the whole period of falling temperature, vaporization bears a larger share of the total heat elimination than it does under normal conditions.

We still need more information regarding the manner in which the body temperature rises when there is no chill or other muscular activity to produce the extra calories necessary to warm the body. A number of observations were made

¹ Hamilton and Barbour: Am. Jour. Physiol., 1925, 73, 321.

in typhoid fever by Coleman and Du Bois¹ and in tuberculosis by McCann and Barr² but they are all a little too short to give us a complete picture. They show, however, in the majority of instances, the heat production rising in gradual steps set at a level distinctly higher than the heat elimina-

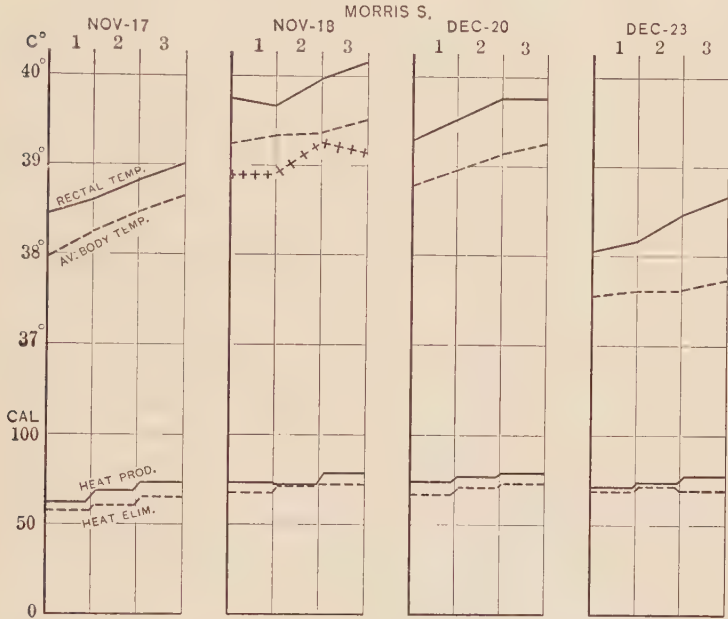


FIG. 87.—Experiments on typhoid patient with rising temperature showing an increasing heat production which outweighs the increasing heat elimination. The uppermost continued line shows the rectal temperature; the dash line, the average body temperature changes. This latter line is arbitrarily started 0.5 degrees below the rectal line. The line of crosses gives the "surface" temperature in one experiment. The lower continued line shows the heat production; the dotted line, the heat elimination.

tion which also rises in steps. In four instances (Fig. 87) the heat production was almost level during the experimental period and the greater part of the rise must have occurred before the experiment was started. This rise is probably caused by the chemical regulation first described by Rubner and discussed by Lusk.³ We do not know the exact mechan-

¹ Coleman and Du Bois: Clin. Cal. 7, Arch. Int. Med., 1915, 15, 887.

² McCann and Barr: Clin. Cal. 29, Arch. Int. Med., 1920, 26, 663.

³ Lusk: The Science of Nutrition, third edition, 1917, p. 141. Saunders & Company, Philadelphia.

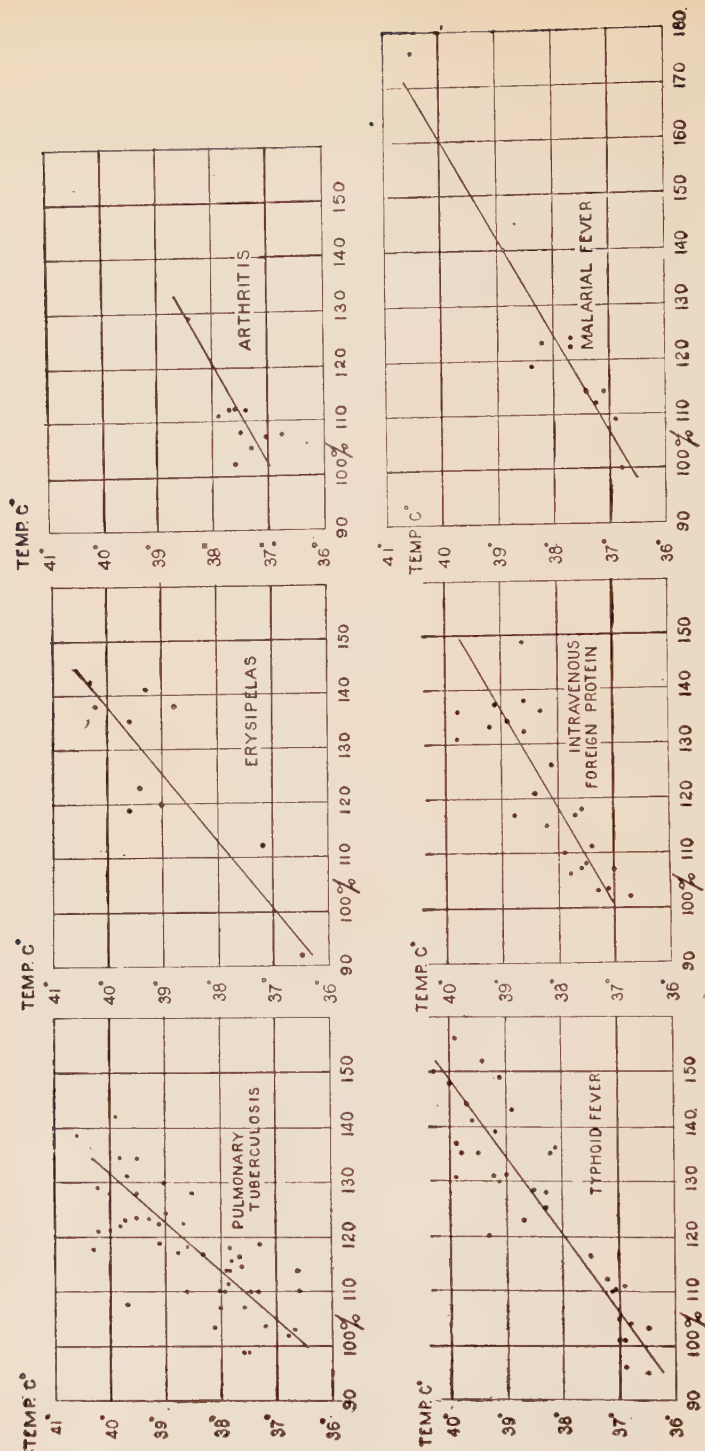


FIG. 88.—Relationship of basal metabolism to temperature in various fevers. Ordinates represent rectal temperature in degrees C.; abscissæ, the metabolism expressed in percentages of the average normal, *e. g.*, 150 equals 50 per cent above the average. Each dot represents a calorimeter experiment of from one to three hours at a given temperature. (From Du Bois *Endocrinology and Metabolism*, D. Appleton & Co., New York.)

ism of this stimulation in fever. The restriction of heat elimination is evidently not so marked as during a chill and the rise in body temperature is more gradual.

THE BASAL METABOLISM IN VARIOUS FEVERS.

The various infections manifest great differences clinically and we should expect to find differences in basal metabolism. It is, therefore, with some surprise that we note the striking uniformity shown in the Sage publications previously mentioned.¹

In comparing these, it will be noted that in pulmonary tuberculosis, there is a tendency for the metabolism to be relatively lower than with corresponding degrees of temperature in other infections. This seems to be due to the fact that phthisis is often accompanied by high fever with comparatively slight toxemia and little or no toxic destruction of protein. The other fevers give rather uniform results and we can say that the average rise in heat production is about 13 per cent for each degree C. (7.2 per cent for each degree F.). It is interesting to note that Sturgis² found about this same per cent increase in the basal metabolism of his exophthalmic goiter patient during an attack of tonsillitis. This general uniformity of rise in metabolism enables us to calculate approximately the total metabolism of a fever patient by finding his normal basal and adding the average increase for his degree of fever. In the case of toxic patients with great destruction of body protein there should be an additional 10 per cent added and a similar addition in all other cases taking much food. If the nitrogen elimination is already high, it is doubtful if food causes any appreciable increase in heat production. In restless patients, an additional allowance of 10 to 30 per cent should be made for muscular activity.

van't Hoff's Law.—In the papers of the Russell Sage Institute of Pathology,³ attention was called to the fact that the increase in metabolism with increased temperatures follows van't Hoff's law. For ordinary temperatures this law can

¹ Du Bois: Jour. Am. Med. Assn., 1921, 77, 352; McCann and Barr: Clin. Cal. 29, Arch. Int. Med., 1920, 26, 663-705; Barr, Cecil and Du Bois: Clin. Cal. 32, 1922, 29, 608-634.

² Sturgis: Arch. Int. Med., 1923, 32, 50.

³ Du Bois: Metabolism in Fever, Jour. Am. Med. Assn., 1921, 77, 352; Endocrinology and Metabolism, New York, D. Appleton & Co., 1922, 4, 95.

be expressed as follows: "With a rise in temperature of 10°C . the velocity of chemical reactions increases between 2 and 3 times. In other words, the coefficient is between 2 and 3." This means an increase of 30 to 60 per cent for the 3 degrees rise from 37° to 40°C . Practically all of the fever experiments are within these limits and the average line shows a temperature coefficient of 2.3.

Van't Hoff¹ and Kanitz² give the temperature coefficients for a number of chemical reactions. If we plot these in exactly the style of the fever patients we note that the lines

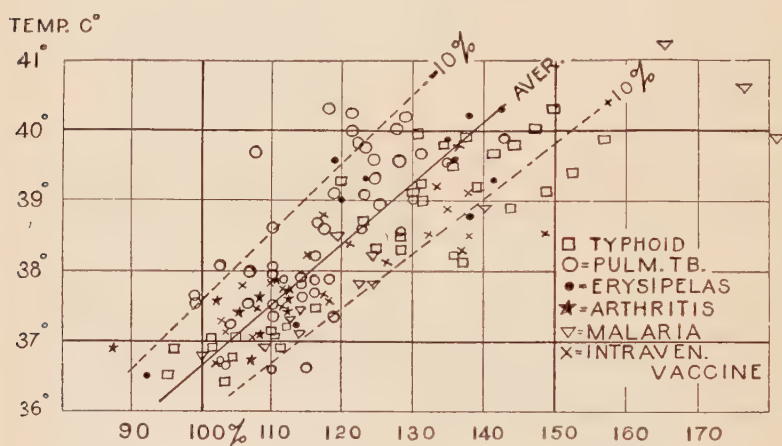


FIG. 89.—Relation of basal metabolism to temperature in six different fevers. The continuous line shows the average and the dotted lines are drawn to represent metabolism 10 per cent above and 10 per cent below the average.

have approximately the same slope. In other words, the reactions in a fever patient respond to a rise in temperature in a manner which resembles closely the chemical reactions in a test-tube suspended in a water-bath. There is a tremendous difference between the simple reactions in the test-tube and the complex oxidations in the diseased human body and we should hesitate to compare them were it not for the large number of biological reactions which show temperature coefficients between 2 and 3. Van't Hoff calls attention to the rate of carbon dioxide elimination in plants with a coefficient of 2.5. Kanitz gives a long list of similar coefficients

¹ Van't Hoff, J. H.: *Studies in Chemical Dynamics*, translated by T. Ewan, Easton, Pa., Chemical Pub. Company, 1896.

² Kanitz: *Temperatur und Lebensvorgänge*, Berlin, 1915.

for plant respiration, rate of isolated hearts, contraction of smooth muscle and the metabolism in cold-blooded animals. Bayliss¹ has warned against interpreting biological phenomena in terms of van't Hoff's law and his masterly discussion should be read by all who are interested in this subject.

Miscellaneous Infections.—It is difficult to make respiration experiments on patients with lobar pneumonia on account

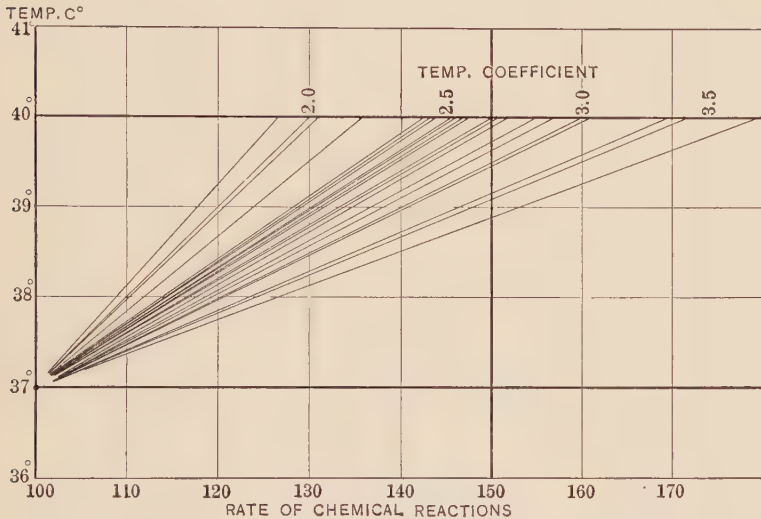


FIG. 90.—The lines in this chart represent a number of typical chemical reactions taken from van't Hoff and Kanitz. The slope of the lines shows the increase in the rate of the reactions as the temperature is raised. Note that the lines correspond closely to those which represent the total oxidations in the human body.

of the coughing and dyspnea. A few experiments, however, have been performed by Kraus,² Riethus,³ Svenson,⁴ Grafe⁵ and Rolly.⁶ These have found in lobar pneumonia increases of 20 to 50 per cent in metabolism and in 1 case a rate 70 per cent higher than normal. The respiratory quotients tend to be very low during the febrile period and much higher in convalescence. In general, it seems that the respiratory

¹ Bayliss: Principles of Gen. Phys., second edition, London, 1918, p. 41.

² Kraus: Ztschr. f. klin. Med., 1891, 18, 160.

³ Riethus: Arch. f. exp. Path. u. Pharmkol., 1900, 44, 239.

⁴ Svenson: Ztschr. f. klin. Med., 1901, 43, 86.

⁵ Grafe: Deutsch. Arch. f. klin. Med., 1911, 101, 209.

⁶ Rolly: Deutsch. Arch. f. klin. Med., 1911, 103, 93.

metabolism in lobar pneumonia rather closely resembles that of severe typhoid fever.

Nitrogen Metabolism in Pneumonia.—The nitrogen and chloride metabolism in pneumonia differs strikingly from that

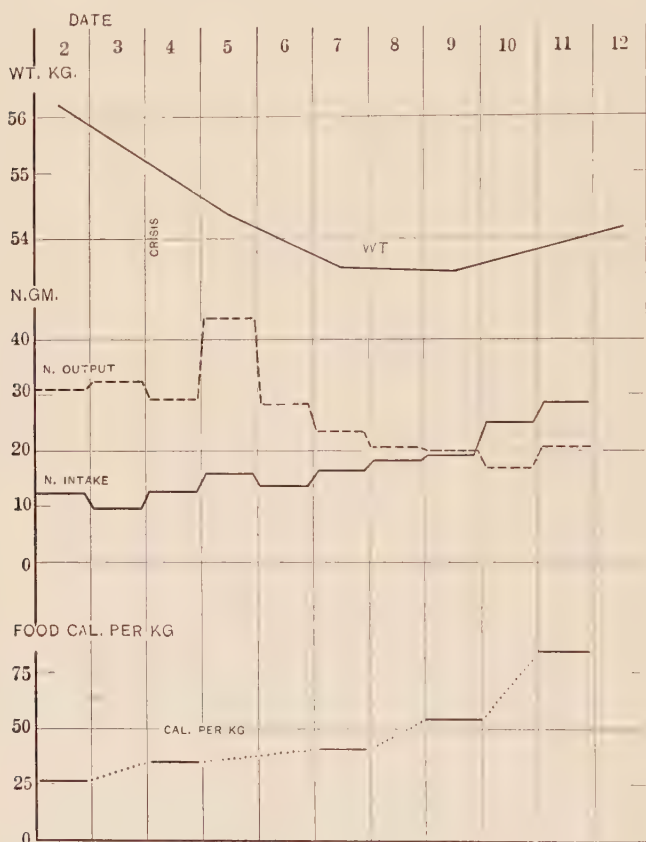


FIG. 91.—Metabolism experiment by Svenson on patient with lobar pneumonia. The line of dashes shows the nitrogen excretion including the nitrogen of the feces which averaged 3 grams a day. Note that the urinary nitrogen rose to 40.8 grams the day after the crisis. At the same time there was a rapid fall in body weight, although the patient was receiving in his food almost enough calories to cover his requirement. (Chart from Du Bois *Endocrinology and Metabolism*, D. Appleton & Co., New York.)

in other fevers. After the crisis many patients show a sudden increase in nitrogen elimination which is usually ascribed to the resolution of the pneumonic exudate with its rich protein content. The accompanying chart of an experi-

ment of Svenson's shows this clearly. During the period of consolidation there is evidently a considerable accumulation of nitrogenous products in the consolidated lung. Löning¹ found by analysis in a pneumonic right lung 41.4 grams of total nitrogen while the opposite normal lung contained only 11.3 grams. Kocher² using a diet containing 3400 to 4200 calories and 2 to 4 grams of nitrogen was not able to reduce the nitrogen excretion below 7 grams a day in one patient and 19.5 grams in the other. In this second patient the excretion remained high until the fifth day of normal temperature. More recently Lauter and Jenke³ have obtained figures almost within normal limits in croupous pneumonia when the temperature was low.

There is an additional source of nitrogen loss in the sputum which Lanz⁴ has found to contain from 0.3 to 1.7 grams of nitrogen a day.

Chloride Metabolism in Fever.—The excretion of chloride is diminished in almost all fevers, malaria being a notable exception. In pneumonia the urine often contains exceedingly small amounts or none at all. This is partly due to the small amount of salt in the fever diet, but the elimination remains low even when the diet contains considerable amounts of salt. The chloride content of the consolidated lung will only explain a fraction of the retention. It has been found that the chloride in the blood of pneumonic patients is usually below the normal "threshold" value of 5.6 grams per liter. This accounts for the absence of chlorides in the urine, since the kidney does not excrete them until they rise above the "threshold" value in the blood. We have no explanation of the low chlorides in the blood and we do not yet know in what part of the body the chlorides are stored.

Metabolism in Tuberculosis.—We have shown in a previous diagram the results in tuberculosis obtained by McCann and Barr in the calorimeter. These confirm the previous findings of Grafe⁵ and Rolly⁶ and others. Barbour⁷ noted a normal metabolism in 3 tuberculous patients in the course of his

¹ Löning: *Klin. Jahrb.*, 1908, **18**, 199.

² Kocher: *Deutsch. Arch. f. klin. Med.*, 1914, **115**, 82.

³ Lauter and Jenke: *Deutsch. Arch. f. klin. Med.*, 1925, **146**, 323.

⁴ Lanz: *Deutsch. Arch. f. klin. Med.*, 1896, **56**, 619.

⁵ Grafe: *Deutsch. Arch. f. klin. Med.*, 1909, **95**, 543.

⁶ Rolly: *Deutsch. Arch. f. klin. Med.*, 9111, **103**, 93.

⁷ Barbour: *Arch. Int. Med.*, 1919, **24**, 624.

studies on antipyretics. Kocher¹ has reported normal figures in a series of 15 afebrile tuberculous patients studied at the Trudeau Sanatorium. Grafe,² however, found an increase in metabolism of 20 to 36 per cent in 7 out of 10 patients with severe, non-febrile, open pulmonary tuberculosis. The cause of this rise in metabolism is not clear unless we accept McCann's³ suggestion that it was impossible for the patients to remain motionless during the experimental periods of four to seven hours. Grafe has also found an increase of 50 to 75 per cent in 3 very severe cases with a temperature over 39° C. The nitrogen excretion in tuberculosis is lower than in other infections and a minimal nitrogen excretion of 2.5 to 9.4 grams may be established.⁴ This is higher than normal but much lower than in typhoid fever or pneumonia. McCann and Barr⁵ studied the specific dynamic action following the ingestion of a meal consisting of 350 grams of chopped meat which contained 70 grams of protein and 28 grams of fat. In 2 tuberculous patients the increase in metabolism during the first three hours after this food amounted to 16 and 18 per cent. The normal controls gave practically the same rise, averaging 21 per cent. This increase in oxidation processes throws additional work on the heart and lungs and may perhaps act like mild exercise in slightly raising the body temperature. McCann⁶ has shown the effects of carbohydrate and protein in increasing the volume of respiration as well as the total metabolism. One hundred grams of cane sugar causes a high quotient and a particularly great increase in the carbon dioxide elimination so that the pulmonary ventilation is increased 60 per cent; 70 grams of protein causes little change in the quotient and the ventilation is increased only about 25 per cent. On the other hand, 140 grams of fat with 1302 calories has but slight specific dynamic action and increases the ventilation only 12 per cent. McCann points out that this is an experimental confirmation of the correctness of the older clinical writers who on empirical grounds urged the importance of fat in the diet.

¹ Kocher: *Calif. State Jour. Med.*, 1921, 19, 430.

² Grafe: *München. med. Wchnschr.*, 1920, 67, 1081.

³ McCann: *Calorimetry in Medicine*, Williams & Wilkins Company, Baltimore, 1924, (Also in *Medicine*, 1924, 3, 1.)

⁴ McCann: *Arch. Int. Med.*, 1922, 29, 33.

⁵ McCann and Barr: *Clin. Cal.* 29, *Arch. Int. Med.*, 1920, 26, 663.

⁶ McCann: *Am. Rev. Tuberc.*, 1922, 5, 870.

Cholera.—Unfortunately, we have no studies of the respiratory metabolism in Asiatic cholera. This disease is accompanied by such a profuse diarrhea that there is a striking dehydration of the tissues and diminution of the urinary secretion. Acute nephritis with anuria is not uncommon and a clinical picture of uremia is frequently encountered. These patients often resemble diabetics in coma, showing very high alkaline tolerance. Striking therapeutic results are obtained by the administration of alkalis and large amounts of water intravenously and subcutaneously.

Syphilis.—The metabolism in syphilis has not been extensively studied but it does not seem to depart from the normal. I cannot find any studies of the basal metabolism of this important malady. Cedarkreutz,¹ a Finnish dermatologist, found the nitrogen minimum only slightly raised above the normal except in 1 patient with fever whose minimum was 7.3 grams. These experiments with Landergren's method of specific nitrogen-hunger followed shortly after Landergren's original studies and antedated by many years the use of this method in other medical clinics.

In scarlet fever there is a high nitrogen elimination and sometimes a considerable retention of sodium chloride.

Acute rheumatic fever in general resembles typhoid.

Diet in Fever.—We have discussed in the previous pages the manner in which we may estimate the total food requirement of fever patients. The clinician must decide for himself how much food he desires to administer. In order to do this intelligently he should consider the changes in metabolism which occur with various types of diet. In all severe infections it is so difficult to establish nitrogen equilibrium that we are usually forced to accept considerable losses of body protein. Moderate daily losses are not harmful unless continued over a period of several weeks. There does not seem to be any particular advantage in giving more than 12 grams of nitrogen (75 grams of protein) in the diet. Carbohydrate is the best sparer of body protein and the best preventive of acidosis and should provide about one-half of the calories, though there is no proof that it does not do as well when it furnishes one-quarter of the calories. Fat in the diet seems to have no harmful effects and it spares the combustion of body fat.

¹ Cedarkreutz: Stickstoff-Wechsel in der Frühperiode der Syphilis, Breslau, 1902.

On theoretical grounds we should give enough calories to cover the total expenditure of energy. If we wish to prevent all loss of body protein we must give from 50 to 100 per cent more calories than the calculated heat production, but it is doubtful if this is necessary or advisable. As a rule there is great difficulty in persuading the patient to take more than one-half of his requirement. The appetite is poor, the patient does not want to be bothered and we hesitate to disturb him. On the other hand, in such a disease as typhoid fever, if we persist in forcing food for a few days, we can greatly diminish the nervous manifestations and improve the general condition. In many fevers the stomach is so upset that food cannot be retained, in others, food seems to increase abdominal distention. When patients with high fever are on low diets we must remember that there is a melting away of body protein and body fat with great loss in weight. We have no actual evidence as to whether or not resistance to infection is actually diminished, but we cannot help believing that the weakness of partial or complete starvation is a serious menace. Patients who end their fever after serious losses of body fat and protein must face a prolonged convalescence.

In comparatively short infections, such as lobar pneumonia, it does not seem necessary or practical to give large amounts of food. In this disease, abdominal distention is a serious complication but it is quite possible that this might be controlled if a suitable diet is devised. Coleman and the writer,¹ while studying typhoid fever, alternated three-day periods of high-fat diet and similar periods of high-carbohydrate diet. It was found that certain patients who had shown diarrhea or distention on a high-fat diet were greatly improved by a change to a high-carbohydrate diet. Other patients who had shown the same phenomena on high carbohydrates were similarly relieved by changing to high fats. Torrey² studied the fecal flora of these patients and found that it varied greatly with the diet. This may be the explanation of improvement caused by the changes. He also found that patients exhibiting an initial fermentative flora of the aciduric type adapted themselves more readily to the high-calory diet of Coleman, as shown especially by a comparative freedom from distention, than did patients with floras of

¹ Unpublished.

² Torrey: *Jour. Infect. Dis.*, 1915, 16, 72.

putrefactive tendencies and they showed a greater tendency to run a mild course. Torrey studied especially the *Bacillus acidophilus* and Coleman has used culture of this organism in typhoid fever with marked success.

Importance of Good Nursing.—The proper administration of a liberal diet in fever depends upon the knowledge of the physician and the experience, tact, and intelligence of the nurse. It is perfectly extraordinary how much food can be given to fever patients by a good nurse. In the first place, she takes scrupulous care of the mouth and teeth, realizing that no patient cares for food if his mouth is dry, his tongue cracked and his teeth dirty. She also takes care of the nose because if this is clogged the patient is forced to breathe through his mouth which soon becomes dried and parched. She sees that the bowels are thoroughly emptied each morning, using enemas if necessary. She studies the likes and dislikes of the individual patient and does not try to force foods which are distasteful even in health. She makes skilful use of substances such as lactose which can be added to liquid foods in such a manner that their presence is not detectable by the patient. She seizes opportunities at night to feed the patient when he is awake. Above all, she uses tact and employs persuasion or gentle firmness as the case demands. With a well-trained nurse the physician need do little more than state how many calories he desires to give with the proportions of protein, fat and carbohydrate. With a nurse who has not had such special training, the physician must spend considerable amount of time in patiently teaching her the general principles. He must encourage her by calculating each day the total calories administered and he must check up the results by examining the mouth, the abdomen and the stools. It is advisable to comment on these every day to the nurse and if they are satisfactory the word of praise should never be omitted. Using these methods in the general wards of Bellevue Hospital practically all of the typhoid patients show mouths and tongues as clean as those of normal men. Almost all of them read the newspaper every day.

The most important constituent of the fever diet has no caloric value. I refer to water, which must be given in large amounts. The more we give the better. While it is some help to have the nurse chart the amounts given it is much more important to chart the amount of urine and insist that this shall never be allowed to become high colored and concentrated.

CHAPTER XVIII.

THE WATER METABOLISM.

WE have seen in a previous chapter that water is formed in considerable amounts from the oxidation of proteins, fats and carbohydrates. It is of importance to study the function of water in the regulation of body heat. There is still a curious amount of ignorance and misconception on the part of physicians regarding the substance which furnishes 60 to 70 per cent of the body weight. For an excellent review of this whole subject, the reader is referred to Rowntree's¹ discussions of the water balance of the body.

There are three main sources of water to the body. First, and most obvious is the water consumed as such or in other liquids, second, but not less important, is the water contained in the so-called solid foods. Finally, there is the water of combustion which plays a part absolutely ignored by most investigators. A glance at a table showing the percentage of water contained in various foodstuffs proves that the distinction between solid and liquid foods is arbitrary, depending more upon the envelope than the chemical composition of the contents. The dietitian would call a tomato solid food, in spite of the fact that it contains a larger percentage of water than does milk. As a matter of fact, milk becomes a solid food in the stomach, as any one can see from the casual inspection of vomitus. On the other hand, a hard biscuit may be softened to such an extent that it resembles in its constituency the milk before coagulation.

In this connection, we may recall the fact that guinea-pigs and rabbits can live for years without drinking water. In cold weather, some people drink but little water, distinctly less than they void in their urine.

As a rule, the kidneys excrete somewhat more than one-half the water eliminated from the body, but in some instances, the urine furnishes only a small percentage of the total elimination. The moisture content of the stools varies greatly

¹ Rowntree: *Physiol. Rev.*, 1922, 2, 116.

and in severe diarrhea, the water losses from this source are enormous. Excessive sputum or purulent discharge may abstract enough water to be of significance. Vomiting can cause serious depletion of the water reserves. All of these put together may be exceeded by the loss of water from the skin and lungs.

The nasal passages are so constructed that they almost completely saturate the inspired air at a temperature close to that of the body. If a person were living in an atmosphere at body temperature completely saturated there would be no water lost through this channel. As the temperature of the saturated air falls it contains less and less water and at 22° C. holds only half as much as at 37° C. A decrease in the water content of the inspired air naturally results where the humidity (percentage saturation) is reduced and air at 22° C. (72° F.) with a 50 per cent humidity contains only one-quarter as much moisture when it enters the nose as when it leaves. Rubner¹ and Benedict² have shown that under ordinary conditions 250 to 400 grams may be lost in this manner per day. The figure is increased by a greater rate of respiration, lower air temperature or lower humidity. There is also a slight increase when the body temperature is raised by fever.

TABLE 76.—RUBNER'S TABLE OF WATER LOSSES.¹

Temp., degrees C.	Water absorbed by dry air.		Water absorbed by moist air.	
	Lungs.	Skin.	Lungs.	Skin.
15	16.8	9.5	9.0	
20	17.0	37.1	11.7	3.6
25	18.4	57.0	10.9	13.0

Water Elimination from Skin.—The elimination of water from the skin resembles to a certain extent that from the respiratory passages. Our integument is slightly moist, somewhat moister than a dead animal, not as moist as the meat in a butcher shop. Under ordinary conditions, the sweat glands do not functionate but there is a passage of water from the blood containing cutis through the comparatively thin epidermis. Evaporation is increased by low humidity of the air, high temperature of the zone in contact

¹ Rubner: Arch. f. Hyg., 1890, **11**, 137, and 1898, **33**, 151.

² Benedict, F. G.: Carnegie Institution of Washington Publication No. 203, 1915, p. 373. Benedict and Carpenter: Carnegie Institution of Washington Publication No. 126, 1910.

with the skin and a rapid exchange of the air bathing the skin. Clothing affects all of these factors. The matter has been carefully studied by Rubner, Wolpert and others from the standpoint of personal hygiene. Their work and that of Schwenkenbecker in clinical cases has been reviewed by Soderstrom and Du Bois,¹ who have made comparative studies of the water eliminated through skin and lungs by a large number of individuals under the standard conditions of the Sage respiration calorimeter. They found that for an average temperature of 22° to 25° C. and 30 to 50 per cent humidity normal men and patients with various diseases lost on an average 24 per cent of their calories through the vaporization of water. The loss per day averaged 700 grams. It will be noted that various diseases with circulatory disturbances, edema, etc., caused but little variation from the normal. Under a large variety of conditions the human body responded to the laws of physics and resembled so much meat. This was all in the absence of the sweat. Similar studies have been made on children by Levine and Wilson.²

TABLE 77.—WATER VAPORIZATION OF DIFFERENT GROUPS OF SUBJECTS STUDIED UNDER STANDARD CONDITIONS OF CLOTHING, TEMPERATURE AND VENTILATION. SUMMARY TABLE.

Group of subjects.	Number of experiments in group.	Percentage of calories lost in vaporization.
13 normal men, ages twenty-two to forty-four years	29	24
6 men after glucose or protein	9	23
4 men after 7 to 10 grains of caffein	5	26
8 boys, ages twelve to thirteen years	8	27
6 old men, ages seventy-seven to eighty-three years	6	27
2 legless men	2	25
2 dwarfs (1 rachitic; 1 achondroplastic)	2	23
3 cretinoid dwarfs	4	22
4 typhoid patients, temperature rising 0.3° to 1° C.	9	22
5 typhoid patients, temperature change less than 0.3° C. during experiment	6	24
1 typhoid patient, temperature falling 0.4° C.	1	28
3 typhoid patients, second to fifth week of convalescence	9	21
5 pernicious anemia patients	6	25
17 cardionephritics and nephritics	24	24
With marked edema	8	25
With slight edema	5	23
With no edema	8	24
With marked dyspnea	6	26
With slight dyspnea	10	23
With no dyspnea	8	25
8 diabetics	30	25

¹ Soderstrom and Du Bois: Clin. Cal. 25, Arch. Int. Med., 1917, 19, 931.

² Levine and Wilson: Am. Jour. Dis. Child., 1926, 31, 323.

When sweating appears, a new factor is suddenly introduced. There is an active instead of a passive transfer of fluid from the interior to the exterior of the body. The surface of the skin may become as moist as the respiratory passages, though not so warm. Sweat in excess of the amount that can be vaporized drips from the skin and removes no heat from the body except as it diminishes body weight.

Sweating is a very different matter from the mere evaporation of water from the non-sweating skin. There seems to be a sudden functioning of the sweat glands whenever the air temperature reaches about 30° to 33° C.¹ or whenever there is a marked discrepancy between the total required heat elimination and the amount which can be disseminated by radiation and conduction and the ordinary vaporization from skin and lungs. Any excess must be taken care of by sweating or else there will be a higher body temperature than is called for by the temperature regulating mechanisms or by the heat center, if indeed, there be one.

Life is possible without sweat glands. A few individuals are born with a congenital absence of these glands combined with various other ectodermal defects. A few of these patients have been studied by Loewy and Wechselmann² and more recently by Richardson³ who has used the Sage Calorimeter and has exposed his patient to different atmospheric conditions. These individuals placed in rooms of various temperatures react like normal persons vaporizing normal amounts of water from the skin until the air has risen above the point when the sweat production usually comes into play. After that, they are unable to dissipate the body heat with sufficient rapidity and the inevitable result is a rise in body temperature.

As yet, we do not know much about the results of sweating induced by nervous or pathological impulses. It would be interesting to study the effect on the heat regulation of the drenching night sweats in tuberculosis. Probably the "cold sweat" caused by fear is so transitory that it causes little disturbance to temperature. Certainly, it does not lend itself well to calorimeter experimentation. The writer has witnessed a similar phenomenon in a patient who felt a sharp

¹ Von Willebrand: *Skand. Arch. f. Physiol.*, 1902, **13**, 337.

² Loewy and Wechselmann: *Arch. f. path. Anat.*, 1911, **206**, 79.

³ Richardson: *Clin. Cal. 40, Jour. Biol. Chem.*, 1926, **67**, 397.

pain in a joint while in a respiration calorimeter. There was such a sudden change in the volume of the closed chamber accompanied by so many fluctuations in the various thermometers that a previously tranquil experiment was terminated abruptly in fear that the apparatus had been broken. When the chamber was opened the patient told of a sudden outbreak of sweating due to the pain.

The phenomena of heat dissipation were discussed under the heading of regulation of body temperature.

The subject of water metabolism is a curious combination of simple laws of physics and practical difficulties in technic. The water content of small articles can be determined with great accuracy but it is extremely difficult to measure satisfactorily the total water intake or output in any metabolism experiment on man. It is much easier to measure the carbon and oxygen than the water. Even if you know the average water content of raw foods, it is almost impossible to cook them in such a manner that you can determine the loss or gain of water. The measurement of the water output involves the determination of the water vapor in the air which is comparatively easy, but there is an important source of error in the rather considerable amounts of water vapor that can be stored in the clothing, bedding, walls of the experimental chamber, etc. We are fortunate if, after the utmost care, our figures are accurate within 5 per cent. Of course, there is a ridiculously large error in any clinical test of the water balance in which the nurse charts down all "fluids" taken as the total intake and records the urine volume as the total output. This usually makes the output 700 to 1000 cc too small. Fortunately, the intake is also made small to about the same degree if the patient is on a diet containing much solid food. It is for this reason that the test is of considerable clinical value in spite of an error of 50 to 100 per cent. One marvels at the manner in which the columns representing intake and output on these charts match so well.

We cannot allow ourselves to believe that the kidneys excrete all the water consumed as "fluids" and that the skin, lungs and bowels take care of all derived from solid foods and the oxidation of carbohydrates, fats and proteins. It is much more accurate and probably close enough for clinical purposes if we chart as intake the total weight of all liquid and solid foods and as output the total weight of urine, feces,

sputum, adding as a basal figure about 700 grams for the water vaporization from skin and lungs, 600 grams in the case of a small person at rest, 800 grams for a large person. We should add to the basal figure a proper percentage for exercise or any other factor which increases the metabolism and make still other additions for sweating, hot weather or a very dry climate. Above all, let us be frank in the realization that our balances are not accurate.

Body Weight.—Our observations on the difficulties of measuring the water balance naturally turn our thoughts to the subject of body weight. Obviously, it is difficult to lose or store water in the body without changing the weight. Water is by all odds the most variable constituent. A man of 70 kilograms contains several kilograms of bones which remain practically constant. His 13 kilograms of dry protein even in starvation can be decreased only at the rate of 40 to 200 grams a day. His 300 to 400 grams of glycogen would supply fuel for about a day. His fat would be diminished 150 to 300 grams in supplying fuel for a whole day. Thus we see that even in starvation it is almost impossible to lose more than 400 to 500 grams of solids in twenty-four hours. Ordinarily people do not change their solid constituents by more than 100 to 200 grams a day. Yet changes in weight of 500 to 1000 grams per day are frequently seen in the clinic even in those who are getting considerable nourishment. The great bulk of this is, of course, water. The 70 kilogram man contains 45 to 50 kilograms of water combined in all sorts of tissues and in the most complex solutions of inorganic salts and organic compounds. Through this body there passes an intermittent stream of water and varying amounts are retained or eliminated according to the physico-chemical condition of the tissues, fluids and kidneys. This is well shown in the chart of Gamble given on page 211.

The body gains weight only during the intake of food and drink. It loses weight intermittently and suddenly during defecation and micturition and loses it constantly and gradually from the vaporization of water from skin and lungs. There is a smaller constant loss from the elimination of carbon dioxide which is almost compensated by the absorption of oxygen from the air. Thus, in a basal calorimeter experiment the normal subject "D," weighing 75.5 kilograms, in a given hour lost 30.7 grams of water and 25 grams of carbon diox-

ide, but absorbed 21.2 grams of oxygen so that his total loss in body weight was only 34.5 grams. Benedict and Joslin,¹ have shown graphically the transient fluctuations in body weight from hour to hour. In their article they call our attention to a Marathon runner who lost $8\frac{1}{2}$ pounds in three hours and a foot-ball player who lost 14 pounds (6.4 kg.) in a game lasting seventy minutes. They calculate that only 100 grams of this could have been solids, $13\frac{3}{4}$ pounds, the remainder, was water, lost chiefly as sweat. We can assume that the thirsty athlete made good this loss in a few hours.

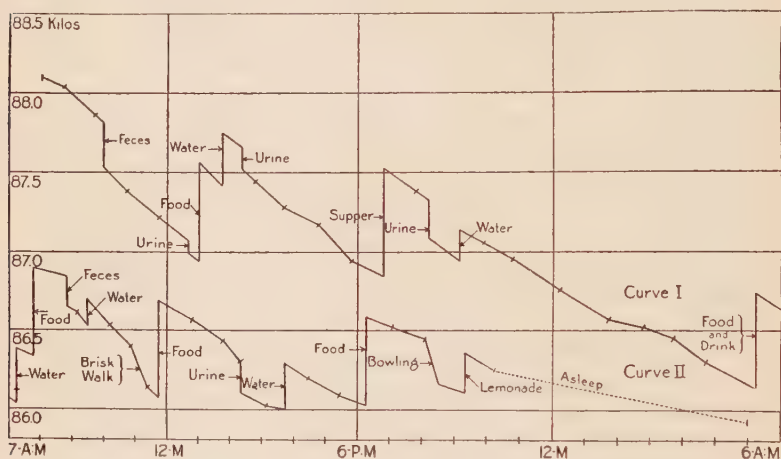


FIG. 92.—Curves showing hourly changes in body weight for twenty-four hours. Curve I shows the change in body weight when the subject was engaged in experimental work and was awake the entire twenty-four hours. Curve II shows the same subject when he worked during the day and slept from 10 P.M. to 6 A.M. (Benedict and Joslin.)

Similar losses in the water content of the body with sudden fall in body weight may occur in severe diarrheas or continued vomiting or in fever patients who are given insufficient amounts of fluids. Such dehydration may be of grave import in adults, but it is particularly serious in the case of infants and loss of water is the cause of much infant mortality. Diabetes mellitus with polyuria unaccompanied by excessive drinking of water may cause temporary water losses in man. Balcar, Sansum and Woodyatt² have clearly shown that it is possible to produce extreme dehydration in dogs by pumping

¹ Benedict, F. G., and Joslin: Carnegie Institution of Washington Publication No. 176, 1912, p. 90.

² Balcar, Sansum and Woodyatt: Arch. Int. Med., 1919, 24, 116.

glucose into the blood faster than it could be utilized by the tissues. In order to get rid of the excess there is a copious diuresis. An extraordinary hyperthermia results.

A gain in the body fluids may be caused by any of the pathological conditions which are accompanied by edema. It would lead us too far afield to discuss this vast problem. In this connection, however, it is necessary to recall the effect of the ingestion of table salt in causing a small retention of water in normal persons and a considerable retention in a certain number of patients with diseased kidneys. Bicarbonate of soda has a similar effect and a diet rich in carbohydrates seems to cause a greater retention of water than one rich in fats. This was well shown in an experiment by Benedict and Milner,¹ who studied a man in a respiration chamber for six days. The routine was exactly the same during the whole period and he rode a stationary bicycle ergometer eight hours each day. There was a great loss in weight on the fat diet. Such a retention from salt or carbohydrate does not usually manifest itself in visible edema and it becomes apparent only when the scales are used. It is difficult to say how great the accumulation of extra fluid in the body must be before it is detected by the eye. In some cases there may be, perhaps, a gain of 2 kilograms without visible edema, in others, a fraction of this amount may become apparent in a puffiness of the eyelids or slight pitting of the shins.

During wasting diseases there is a loss of body protein and fat as well as water. Even the bones suffer to a certain extent. These same substances are replaced in convalescence, sometimes at a most surprising rate.

The gain of weight in obesity is due to the gradual deposition of fat with only slight, if any, increase in body protein. Fatty tissue contains but little water, in fact, it tends to replace water. Obese patients may lose much fat during periods of undernutrition and yet lose no weight because the body stores water. It is interesting to calculate how much of an excess in food is required to produce obesity. The ordinary individual requires about 2500 calories a day. If he consumes 10 per cent more than his energy expenditure over three hundred and sixty-five days he will store in his body a little more than 91,000 calories in the form of about 10 kilograms (22 pounds) of fat.

¹ Benedict and Milner: United States Department of Agriculture Office of Experiment Stations, Bull. 175, 1907, p. 225.

CHAPTER XIX

INFLUENCE OF THE DISEASES OF THE NERVOUS SYSTEM ON BASAL METABOLISM.

THERE has been a large amount of work on the effect of cutting the spinal cords of laboratory animals. This profoundly affects the heat regulation and secondarily the metabolism. A review of this work and other experiments on the nervous system of animals would be out of place and we shall confine our attention to humans. Bornstein¹ and Grafe² made some early observations on patients with insanity, finding, on the whole, normal figures in manic-depressive insanity and somewhat diminished figures in dementia precox.

Bowman, Eidson and Burladge³ studied 10 patients with dementia precox and found that in the first tests 3 were within normal limits and the other 7 ranged from -12 to -31 per cent. Subsequent examinations showed a tendency of the metabolism to rise under treatment. Gibbs and Lemcke⁴ in a series of 11 patients with this form of insanity found 2 slightly above the normal zone and the remainder from 5 to 32 per cent below the average normal. In the manic-depressive group almost all the results were within the normal limits. Whitehorn and Tillotson⁵ also found a tendency toward low values in dementia precox. Bowman and Grabfield⁶ noted a somewhat lowered metabolism in almost all of the 50 patients with various forms of insanity on whom tests were made. This perhaps was due to the sedentary lives of the insane. Levine⁷ working with disabled veterans noted a metabolic rate more than 10 per cent above the average normal in about one-fifth of his patients with hysteria, neurasthenia and anxiety neurosis.

¹ Bornstein: *Monatschr. f. Psychiat. u. Neurol.*, 1908, **24**, 392.

² Grafe: *Deutsch. Arch. f. klin. Med.*, 1911, **102**, 15.

³ Bowman, Eidson and Burladge: *Boston Med. and Surg. Jour.*, 1922, **187**, 358.

⁴ Gibbs and Lemcke: *Arch. Int. Med.*, 1923, **31**, 102.

⁵ Whitehorn and Tillotson: *Boston Med. and Surg. Jour.*, 1925, **192**, 1254.

⁶ Bowman and Grabfield: *Arch. Neurol. and Psychiat.*, 1923, **9**, 358.

⁷ Levine: *Jour. Lab. and Clin. Med.*, 1923, **8**, 775.

Grafe¹ has recently reviewed the whole subject of the influence of nervous diseases and changes in muscle tonus. He speaks of our lack of knowledge as to the extent of the increases found in the agitated and in the delirious, when they are exhibiting violent muscular activity. He points out that in such cases the muscles may act with abnormal economy on account of training and constant use. Such cases do not seem to require a large food intake to maintain weight. Magnus-Levy² found in one patient with paralysis agitans a distinct increase in metabolism which disappeared when the tremor was stopped by means of hyoscin. Grafe,³ however, studied tremors of various forms and found that the metabolism exceeded the normal limits only if the tremors were very pronounced. He believes that in patients with chronic tremor the muscles work more economically than in the case of voluntary contractions. This may be the result of training, possibly there are compensatory diminutions of metabolism in other parts of the body. In this connection it is interesting to recall the surprisingly low expenditure of energy during childbirth.

Kauffman⁴ was able to study a man during an epileptic attack and found, as might be expected, a great increase in metabolism. Bornstein⁵ thought that the increase in metabolism sometimes lasted for many hours after the attack, but his later work with Stroman⁶ showed that this was not always the case. Talbot, Hendry and Moriarty⁷ in a study of 11 epileptic children between the ages of eight and a half and thirteen and a half years found the basal metabolism either normal or slightly elevated and they warn against the use of thyroid extract in the treatment of this disease. Talbot⁸ has noted a low basal metabolism in some Mongolian idiots and in one infant with complete absence of the cerebral hemispheres and in one child with amaurotic familial idiocy. Grafe⁹ in studying katatonic stupor found a considerable

¹ Grafe: *Ergeb. der Physiol.*, 1923, 21, Part II, 1.

² Magnus-Levy: *Ztschr. f. klin. Med.*, 1906, 60, 214.

³ Grafe: *Deutsch. med. Wchnschr.*, 1921, 47, 147.

⁴ Kauffman: *Beiträge zur Pathologie des Stoffwechsels bei Psychosen*, II Epilepsie 51, Jena, 1908. This article was not accessible in New York. Ref. by Grafe.

⁵ Bornstein: *Monatschr. f. Psychiat. u. Neurol.*, 1908, 42, 392.

⁶ Bornstein and Stroman: *Arch. f. Psychiat.*, 1910, 47, 154.

⁷ Talbot, Hendry and Moriarty: *Am. Jour. Dis. Child.*, 1924, 28, 419.

⁸ Talbot: *Monatschr. f. Kinderheilk.*, 1924, 27, 465.

⁹ Grafe: *Deutsch. Arch. f. klin. Med.*, 1911, 102, 15.

diminution of metabolism below the normal in such patients, even though there was a generalized rigidity. He concluded that the increased muscle tonus was apparently without significance for the level of oxidation since the hypertonic muscle performed just as little work as the hypotonic and that the accomplishment of external work was the really important factor. In 4 out of 10 of these katatonic patients the metabolism was distinctly low, even going to 31 per cent and in 1 other patient whose stupor was not quite certainly of katatonic origin the figure was 39 per cent below the average, a level which is only expected in myxedema or profound undernutrition.

The work of Grafe and Traumann¹ on hypnotic rigidity is interesting in this connection. They found no increased metabolism in the kataleptic rigidity during hypnosis, while the repeated voluntary contractions of the same muscle groups increased the heat production 50 per cent. They noted that increased tension in itself caused little or no expenditure of energy and led to no increase in oxidation.

Grafe's work on the muscles was not substantiated by the investigations of Schill² who found that in katatonic patients, who held their arms or legs stiffly in one position during the experiments, there was the same static work as in normals accompanied by the same rise in oxygen consumption, pulse-rate, etc.

The more recent work by Grafe³ included tonus anomalies of men with encephalitis lethargica, flaccid paralysis and pyramidal tract disease and demonstrated normal heat production in the cases with muscle rigidity where there was no motor activity or chronic contractions. In fact the average for all the tests was 0.5 per cent below the normal level.

The Influence of Mental Activity on Metabolism.—We turn again to the excellent discussion in Grafe's monograph. The brain comprises only 2 per cent of the total body weight, but it has 10 times as large a blood flow as the same mass of skeletal muscle. Grafe estimates that this organ contributes 6 to 10 per cent of the total resting metabolism. The fact that metabolism falls during sleep in certain cases, as we have shown in another place, is perhaps due in part to a diminished

¹ Grafe and Traumann: *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1920, orig., 62, 237.

² Schill: *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1921, 70, 202.

³ Grafe: *Deutsch. Arch. f. klin. Med.*, 1922, 139, 155.

metabolism of the brain, but there is no direct evidence substantiating this. Even more confusing is the evidence concerning the effect of mental work on the total metabolism. Speck¹ in 1882, found that his metabolism increased 8 to 10 per cent during mental work, but ascribed this to small muscular movements. Loewy² and Johansson confirmed his results. Benedict and Carpenter³ studied 22 young men during examinations and found the metabolism very slightly greater than when they were performing an equal amount of work that required no mental effort. Becker and Olsen⁴ made a long and careful study of the respiration and carbon dioxide elimination during mental work. They found that on merely keeping the eyes closed there was a diminution in the volume of air exhaled and in the carbon dioxide also. When the subjects memorized meaningless syllables there was an increase in the CO₂ elimination. This increase which was large at the beginning of work they attributed in part to a diminution of the store of CO₂ in the body (*Auspumpung*). They believed that a fraction might arise from muscular movements but that there was also a true increase in metabolism which was parallel to the amount of mental work performed as estimated by the subjects themselves. Practice seemed to reduce the increase in metabolism required for a given piece of work. It is unfortunate that the Danish investigators did not study the oxygen consumption since the CO₂ does not give a reliable index of the metabolism under changing conditions.

Grafe concludes that intensive mental effort probably has an influence on metabolism but that up to the present time the observations have been too small in number and too conflicting in their findings to decide this question definitely.

The Effect of Strong Emotions.—Grafe speaks of the effect of the war in Germany in causing a loss of weight, even in the classes where there was no change in the food or mode of life. This, of course, might be due to a loss of appetite. He also cites the case of a doctor who for a long time, during a metabolism experiment, kept himself at the same weight on a con-

¹ Speck: *Arch. f. exp. Path. u. Pharmakol.*, 1882, **15**, 81.

² Loewy: *Berl. klin. Wchnschr.*, 1891, **28**, 434. Johansson: *Skand. Arch. f. Physiol.*, 1898, **8**, 105.

³ Benedict and Carpenter: United States Department of Agriculture Office of Experiment Stations, *Bull.* 208, 1909.

⁴ Becker and Olsen: *Skand. Arch. f. Physiol.*, 1914, **31**, 81.

stant diet which was measured daily. In the midst of the experiment he received bad news of such threatening import for him and his family that he was anxious and depressed all day long. In spite of the fact that he continued his work and his diet as before, the weight which had previously been constant dropped 2 kilograms in a few days.

Grafe and his associates¹ have approached this puzzling question by means of hypnosis. They made a series of experiments on young normal men and women, suggesting to them, while under hypnosis, the most terrible calamities, such as the death of relatives, amputation of arms, fights with cannibals, etc. In 4 experiments there was either no change or else a slight depression in metabolism, but in 9 there was an increase ranging from 5 to 25 per cent, the average for the whole series being 7.6 per cent. Two young men who were told that they had won large sums in lotteries and were living in luxury showed an increase of 4 per cent. Grafe believes, and I think with good reason, that this is the first good evidence that emotion may cause a distinct increase in metabolism. His subjects showed no increases in respiration or heart action which would account for the change. He believes that there was a general alteration in the organs as the result of the stimuli from the centers in the brain passing out to the periphery chiefly by means of the synthetic nervous system, as well as some increase in the metabolism of the brain itself. Aub² has suggested that increases in metabolism from emotion are due to an increased secretion of epinephrin according to the emergency theory of Cannon.³

In 2 patients with paralytic stupor Grafe⁴ found the metabolism reduced 20 per cent in 1 and normal in the other. Bornstein⁵ had previously obtained normal figures in 2 such patients.

Probably everyone who has had much experience in basal metabolism tests has noticed an increase in oxygen consumption respiration and pulse-rates if the subject of the experiment becomes uncomfortable or excited. My first striking

¹ Grafe and Traumann: *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1920, orig., 62, 237. Grafe and Mayer: *Ztschr. f. d. ges. Neurol. u. Psychiat.*, 1923, 86, 247.

² Aub: *Jour. Am. Med. Assn.*, 1922, 79, 95.

³ Cannon: *Bodily Changes in Pain, Hunger, Fear and Rage*, New York, D. Appleton & Co., 1915.

⁴ Grafe: *Deutsch. Arch. f. klin. Med.*, 1911, 102, 15.

⁵ Bornstein: *Monatschr. f. Psychiat. u. Neurol.*, 1908, 24, 392.

demonstration of this was in 1914 when the exophthalmic goiter patient, Max W. was in the calorimeter. During one hour his metabolism rose 10 per cent and we were unable to discover the cause until he told us that he had seen through the calorimeter window a person whom he disliked intensely. A most interesting note on such rises in metabolism has recently been made by Hafkesbring and Collett¹ who studied the metabolism of 2 normal women over a long period. They discovered that harsh or sudden noises increased the oxygen consumption about 10 per cent. One young woman recovered in about five minutes, the other often required fifteen or twenty minutes. They also observed that fatigue if not associated with nervousness sometimes reduced the metabolism. Landis² also noted that strong emotions usually cause an increase in the metabolism although there is sometimes a decrease.

Even more striking results have been obtained by Ziegler and Levine³ working with war veterans suffering from hysteria, neurasthenia or anxiety neurosis. First a basal metabolism test was made under the usual conditions. Then the veterans were told to think of their army experiences and particularly the most disagreeable ones. In 3 cases there was a fall in metabolism, in 1 no change, but in 11 there was a marked rise. A third test made after the effect of the emotion had worn off showed a return to the original level of heat production.

Some of the men who showed the increased metabolism were not aware of any emotions. Many of the men admitted feelings of repulsion, anger or disgust. The most frequent objective responses were small changes in the color of the skin, slight changes in rate and amplitude of respiration and very fine tremors. The authors emphasize the fact that in some patients there was complete failure to recognize any emotion though readings clearly indicated a rise in metabolism. This, they believe, offers one hopeful explanation for the insidious way in which neurasthenic individuals may dissipate their energy.

¹ Hafkesbring and Collett: *Am. Jour. Physiol.*, 1924, **70**, 73.

² Landis: *Am. Jour. Physiol.*, 1925, **74**, 188.

³ Ziegler and Levine: *Am. Jour. Med. Sci.*, 1925, **159**, 68.

CHAPTER XX.

THE EFFECTS OF DRUGS UPON THE BASAL METABOLISM.

EXCELLENT reviews of the literature of this subject have been made by Barbour in *Endocrinology and Metabolism*, 3, 717 and by McCann¹ in his monograph *Calorimetry in Medicine*. The reader is referred to these for the experiments on animals and for the discussion of the various phases of metabolism which are not reflected in the respiratory exchanges. The extracts of the various endocrine organs have been discussed in the previous chapters.

The drug about which we have most information is caffeine. This has been recognized for a long time as a stimulant to the general metabolism. Studies have been made by Edsall and Means,² Higgins and Means³ and Means, Aub and Du Bois.⁴ Edsall and Means found an increase of 3 to 10 per cent after 0.324 grams subcutaneously of caffeine-sodium-salicylate. Higgins and Means obtained similar results. Means, Aub and Du Bois gave 8 to 10 grains by mouth, approximately 8.6 mg. per kilogram of body weight. This dose is considerably larger than that which is ordinarily given for therapeutic effects. The metabolism was increased 7 to 23 per cent. In the three papers quoted the maximum rise usually occurred in the first hour. There was no consistent change in the respiratory quotient.

Alcohol has been extensively studied by Benedict and his co-workers of the Nutrition Laboratory in Boston. Atwater and Benedict⁵ have shown that over 98 per cent of ingested alcohol is completely oxidized to carbon dioxide and water (see also Atwater, Billings, *et al.* *Phys. Aspects of Liquor*

¹ McCann, W. S.: *Calorimetry in Medicine*, Williams and Wilkins Company, Baltimore, 1924 also in *Medicine*, 1924, 3, 1.

² Edsall and Means: *Arch. Int. Med.*, 1914, 14, 897.

³ Higgins and Means: *Jour. Pharm. and Exp. Therap.*, 1915, 7, 1.

⁴ Means, Aub and Du Bois: *Clin. Cal.* 20, *Arch. Int. Med.*, 1917, 19, 832.

⁵ Atwater and Benedict: *Department of Agriculture Bull. No. 69*, 1899; *Mem. Nat'l. Acad. Sci.*, 1902.

Prob., 1903). Higgins¹ working in the Nutrition Laboratory found that 30 to 45 cc of alcohol caused little or no change in the basal metabolism. In about one-fifth of the experiments there was a rise in heat production of from 5 to 7 per cent. There was no appreciable specific dynamic action, although 20 to 40 per cent of the total metabolism was due to alcohol. Loewy² found a slight decrease in oxygen utilization after morphine administration. Morphine in doses of 16 milligrams was found by Higgins and Means to cause either a slight decrease or no effect at all on the basal metabolism. Barbour, Maurer³ and von Glahn observed a definite depression of oxidation after this dose. Chanutin and Lusk⁴ have pointed out that Higgins and Means obtained diabetic quotients on themselves after therapeutic doses of morphine. They themselves gave two dogs doses of 12 to 29 milligrams morphine per kilogram of body weight and found no depression of quotient. One dog went to sleep and his metabolism fell 6.2 per cent. The other dog manifested increased irritability and heightened reflexes and the metabolism rose 10 per cent. Heroin in 5 milligram doses did not affect the metabolism of Higgins and Means. Strychnine in 0.1 gram doses had no effect. Edsall and Means and Higgins and Means observed a slight increase after the subcutaneous injection of 0.4 to 0.5 grams of camphor. The same authors found a slight increase after 1 milligram of atropine.

The antipyretic drugs have been thoroughly studied. Denis and Means⁵ gave repeated doses of sodium-salicylate to 3 surgical patients, 2 showed no change, but the third gave an increase of 15 per cent in basal metabolism. Barbour⁶ gave 1 gram of acetyl-salicylate acid to a tuberculous patient with a drop of 1° C. in temperature and a fall of 3.5 per cent in metabolism. Barbour, Harris and Plant⁷ after half a gram of quinine found an increased heat production in 2 experiments and no change in 2 others. Means and Aub⁸ found

¹ Higgins: *Jour. Pharm. and Exp. Therap.*, 1917, **9**, 441.

² Loewy: *Berl. klin. Wchnschr.*, 1891, **28**, 434.

³ Barbour and Maurer: *Jour. Pharm. and Exp. Therap.*, 1920, **15**, 305.

⁴ Chanutin and Lusk: *Jour. Pharm. and Exp. Therap.*, 1922, **19**, 359.

⁵ Denis and Means: *Jour. Pharm. and Exp. Therap.*, 1916, **8**, 273.

⁶ Barbour: *Arch. Int. Med.*, 1919, **24**, 624.

⁷ Barbour, Harris and Plant: *Endocrinology and Metabolism*, New York, D. Appleton & Co., 1922, **3**, 768.

⁸ Means and Aub: *Arch. Int. Med.*, 1919, **24**, 404.

that quinine was of no value in reducing the basal metabolism in exophthalmic goiter.

In previous chapters the effects of oxygen have been discussed. Lavoisier and Seguin in 1789 discovered that it had no effect in increasing metabolism. This has been confirmed by Benedict and his associates. On the other hand, low concentrations of oxygen cause an increase in pulmonary ventilation and a consequent rise due to muscular activity. High concentrations of carbon dioxide cause a more striking dyspnea.

Boothby and Rowntree¹ have also published an excellent review of the effect of drugs on the basal metabolism. In making a general survey of the more commonly used drugs, they conducted 54 experiments with 25 different substances. Adrenalin was the only drug which, in the doses used, caused a 10 per cent or more change in the metabolism within two hours of administration. Snell, Ford and Rowntree² have shown that potassium iodide given in large doses over several weeks to patients with normal thyroids, caused no alteration in metabolism. In 3 subjects with small adenomas of the thyroid a marked increase of not less than 20 per cent resulted. It is difficult to explain the fall in metabolism and improvement in symptoms which Plummer³ obtains after giving exophthalmic goiter patients iodine in the form of Lugol's solution. This discovery which has been discussed in a previous chapter is one of the brilliant achievements in modern medicine.

¹ Boothby and Rowntree: *Jour. Pharm. and Exper. Therap.*, 1923, **22**, 99.

² Snell, Ford and Rowntree: *Jour. Am. Med. Assn.*, 1920, **75**, 515.

³ Plummer: *Jour. Am. Med. Assn.*, 1923, **80**, 1955.

INDEX OF AUTHORS.

A

ABERNETHY, 112
 Abbott, 361
 Adams, 274, 278
 Alcott, 352
 Alexander, 311
 Allen, 218, 243, 247, 248, 251, 252,
 254, 258, 269, 273, 275, 276, 277
 de Almeida, 160
 Anderson, 222
 Andersson, 292
 Andral, 139
 Armsby, 190, 195, 236
 Atkinson, 31
 Atwater, 29, 45, 81, 82, 412
 Aub, 33, 43, 49, 126, 152, 169, 199,
 247, 248, 252, 254, 260, 264, 294,
 305, 306, 310, 312, 317, 318, 319,
 324, 330, 342, 343, 355, 358, 365,
 410, 412, 413
 Avroroff, 370

B

BAILEY, C. V., 94
 Bailey, H., 137
 Bakwin, 377
 Balcar, 377, 404
 Baldwin, 126
 Banting, 277, 278, 284
 Barach, 303
 Barborka, 274, 278
 Barbour, 156, 199, 368, 377, 386, 393,
 413
 Bardeen, 126, 188
 de Barenne, 103
 Barker, 363
 Barr, 52, 60, 138, 139, 184, 367, 376,
 381, 383, 387, 389, 393
 Bauer, 180, 224
 Baumann, E., 322
 Baumann, E. D., 25, 26, 30, 318
 Bayliss, 391

Becker, 409
 Bedale, 138, 144, 154, 183
 Beeler, 244, 248, 251, 254, 261, 274,
 275
 Benedict, C. G., 52, 102, 155, 156, 382
 Benedict, F. G., 21, 25, 31, 44, 45, 47,
 49, 51, 52, 76, 77, 81, 82, 89, 94, 97,
 99, 102, 105, 107, 110, 122, 125,
 131, 136, 137, 138, 143, 148, 151,
 152, 153, 154, 155, 156, 162, 163,
 164, 170, 182, 183, 184, 193, 200,
 201, 208, 214, 216, 217, 218, 219,
 231, 242, 243, 245, 248, 251, 254,
 256, 264, 272, 273, 274, 276, 293,
 308, 312, 347, 382, 399, 404, 405,
 409, 412
 Benedict, S. R., 26
 Bergman, 292
 Bergmann, von, 238, 239
 Berheim, 150
 Bernstein, 244, 248, 251, 345
 Best, 277, 278
 Bidder, 194
 Biedl, 291
 Binet, 242
 Binger, 317
 Bleibtreu, 30
 Bloor, 27
 Blunt, 52, 150, 224, 226, 349
 Bogaert, van, 345
 Bohland, 358
 Bonniger, 264
 Boothby, 21, 76, 94, 118, 120, 126,
 148, 177, 204, 205, 226, 232, 244,
 248, 251, 254, 261, 273, 274, 275,
 278, 279, 282, 289, 291, 295, 308,
 319, 323, 327, 331, 340, 343, 344,
 345, 351, 357, 359, 363, 366, 414
 Bornstein, 406, 407, 410
 Bouchard, 113
 Bouchut, 186
 Bowen, 366
 Bowman, 303, 406
 Bozenraad, 235
 Braman, 195, 236

Bright, 318, 319, 343
 Brittingham, 355, 356
 Broca, 113
 Brody, 147, 188
 Brugsch, 208, 215
 Bryant, 29
 Buckman, 361
 Burger, 103
 Burgess, 294
 Burladge, 406

C

CAMERON, 148
 Campbell, J. A., 158
 Campbell, W. R., 284
 Cannon, 317, 410
 Carman, 198
 Carpenter, 47, 49, 51, 75, 78, 82, 92,
 99, 105, 130, 170, 274, 351, 399, 409
 Cathcart, 208
 Cecil, 367, 376, 381, 389
 Cedarkreutz, 395
 Chanutin, 413
 Christian, 343
 Christie, 254
 Chvostek, 291, 356, 358
 Clark, 159
 Clough, 311
 Cohen, 316, 371
 Coleman, 36, 68, 167, 191, 199, 218,
 223, 371, 372, 373, 374, 376, 385,
 387
 Collett, 131, 158, 350, 411
 Collins, 99, 293
 Collip, 278
 Cramer, 307
 Craver, 254
 Cremer, 257
 Crile, 305, 327, 333
 Crofts, 110, 151

D

DANA, 114
 Dalrymple, 134
 Davies, 315
 Delcourt-Bernard, 156
 Denis, 264, 306, 413
 Dethloff, 103
 Douglas, 94, 159
 Draper, 303
 Dreyer, 126, 173, 174, 176, 196, 197,
 204

Drinker, 355, 356
 Du Bois, D., 114, 118, 166, 231, 292
 Du Bois, E. F., 33, 41, 43, 44, 46, 49,
 52, 68, 80, 89, 114, 115, 118, 132,
 133, 138, 139, 152, 153, 156, 163,
 167, 169, 175, 184, 190, 191, 199,
 205, 218, 223, 231, 242, 243, 244,
 247, 248, 249, 251, 252, 253, 254,
 258, 260, 261, 264, 273, 275, 277,
 292, 293, 310, 312, 323, 333, 349,
 355, 356, 362, 364, 365, 367, 368,
 373, 374, 376, 381, 382, 383, 385,
 387, 389, 400, 412
 Dunwiddie, 227
 Durig, 156, 158
 Dusser de Barenne, 103
 Dye, 150, 180, 230, 232, 349

E

EAKIN, 349
 Eckstein, 236, 238
 Edison, 406
 Edsall, 360, 412
 Eggert, 291
 Eijkmann, 159
 Else, 306
 Emery, 256
 Emmes, 68, 99, 153
 Epstein, 310, 347, 366

F

FABER, 125
 Faillie, 113
 Falk, 133, 138, 153
 Falta, 244, 248, 251, 272, 316, 345,
 348
 Fick, 36
 Ficker, 28
 Fisher, 41
 Fitz, 264, 279, 317
 Fitzgerald, 328
 Fleming, 161
 Fletcher, 284
 Folin, 264
 Ford, 344, 349, 414
 Forman, 318, 319, 343
 Foster, 254
 Fox, 77, 105
 Frank, 227
 Fries, 158, 195, 236
 Fubini, 113
 Fulton, 156
 Furusawa, 46, 92

G

GAISBOCK, 361
 Gamble, 208, 211
 Gauvain, 158
 Gavarret, 139
 Georges, 158
 Gephart, 44, 49, 153, 163, 167, 244,
 247, 248, 252, 254, 261, 264, 292,
 349, 373
 Geppert, 20, 90
 Gessler, 131, 156
 Geyelin, 244, 251, 254, 260, 306
 Gibbs, 406
 Gigon, 49
 Glahn, von, 413
 Goetsch, 311
 Göttche, 47, 148
 Grabfield, 303, 406
 Gradinescu, 317
 Grafe, 21, 215, 236, 238, 239, 253,
 256, 264, 277, 291, 344, 348, 355,
 357, 358, 359, 360, 361, 362, 366,
 368, 371, 377, 391, 393, 394, 406,
 407, 408, 410
 Graham, 236
 Grant, 279
 Grau, 156
 Gray, 278
 Greene, 340
 Greenwald, 254
 Greer, 312
 Gruber, 28
 Guillemot, 186
 Gunderson, 359
 Gundobin, 113

H

HÄBERLIN, 158
 Hafkesbring, 131, 158, 350, 411
 Hagedorn, 103, 105
 Haggard, 61
 Haldane, 78, 93, 159
 Halter, 348
 Hamburger, 363
 Hamilton, 386
 Hamman, 306
 Hannon, 100, 251, 257, 260, 262, 268,
 274, 275, 280, 281, 283
 Hannover, 364
 Hanson, 174
 Harris, 413
 Harris, J. A., 148, 152, 153, 162, 170,
 193, 201, 312, 347

Hasselbalch, 137
 Hausleiter, 239
 Hawk, 150, 210
 Helmreich, 103, 107, 237, 312
 Henderson, 61, 78, 159
 Hendry, 99, 143, 407
 Herxheimer, 102
 Higgins, 159, 251, 264, 412, 413
 Hill, A. V., 46, 94
 Hill, L., 158
 Hiller, 366
 Hindhede, 34
 Hirsch, 208
 Hirschfeld, 34
 Hirschlaff, 292
 Hirschman, 306
 Hobson, 173, 177
 Hoeffel, 208
 Holmes, 324, 326, 330
 Holt, 190, 312
 Holton, 245, 252
 Homans, 107
 Hoobler, 138
 Howe, 210
 Howland, 107, 114, 138
 Hubbard, 268
 Hun, 306, 310
 Hunt, 100, 311
 Hyman, 300, 311, 317, 323

I

ISAACS, 361
 Isaacson, 306

J

JANET, 118, 147, 303
 Janney, 254, 306
 Jansen, 222
 Jaquet, 75, 232, 233, 292
 Jenke, 35, 262, 309, 360, 393
 Joffe, 222
 Johansson, 130, 164, 409
 Johnson, 382
 Jones, 100
 Joslin, 218, 243, 244, 245, 246, 248,
 249, 251, 252, 253, 259, 264, 269,
 272, 273, 274, 275, 276, 278, 404

K

KAKEHI, 357
 Kaminer, 348

- Kanitz, 390
 Kassowitz, 195
 Kauffman, 407
 Kendall, 321, 331
 Kern, 227
 Kessel, 300, 311, 317, 323
 Kestner, 158
 Kimball, A. L., 53
 Kimball, O. P., 287, 288
 King, J. H., 216
 King, J. T., 21, 68, 185, 348
 Kitchen, 274, 278
 Klemperer, 34, 371
 Knipping, 103, 161, 354
 Koch, 236
 Kocher, 34, 36, 372, 393, 394
 Kramer, 278
 Kraul, 348
 Kraus, 20, 356, 358, 362, 368, 370, 391
 Krause, 307
 Krogh, A., 46, 128, 151, 153, 154, 162, 174, 187, 191, 206, 258
 Krogh, M., 102
 Kunde, 350

L

- LABBÉ, 345
 Ladd, 252, 259, 263, 268
 Lande, 300, 310, 347, 366
 Landergren, 34, 35, 264
 Landis, 411
 Langworthy, 88
 Lanz, 350, 393
 Larsen, 311
 Lauter, 35, 47, 163, 230, 233, 240, 262, 309, 360, 393
 Laves, 242
 Lavoisier, 18, 159
 Lefevre, 155, 186
 Lehmann, 158, 208, 251
 Leimdörfer, 243, 251
 Lemcke, 406
 Lenhart, 287
 Lennox, 359
 Leo, 20, 251
 Lev, 363
 Levine, 90, 107, 215, 268, 277, 379, 406, 411
 Lewis, 254, 264
 Leyden, von, 371
 Lieb, 317, 323
 Liebermeister, 20, 369
 Liebesny, 180, 233
 Likhatscheff, 370
 Linder, 366
 Lindhard, 46, 157, 162, 258, 315
 Lissauer, 113
 Livierato, 242
 Loeffler, 343
 Loewy, 37, 75, 76, 132, 155, 164, 187, 218, 348, 401, 409, 413
 Löffler, 239
 Long, 46
 Löning, 371, 393
 Loucks, 327
 Luciani, 208
 Lupton, 46
 Lusk, 18, 31, 32, 37, 38, 39, 41, 45, 46, 47, 48, 71, 82, 132, 155, 159, 193, 194, 199, 200, 208, 212, 214, 216, 218, 221, 222, 243, 244, 247, 248, 251, 252, 253, 254, 258, 263, 264, 292, 318, 368, 387, 413
 Lüthje, 348
 Lyman, 100, 279

M

- McALPIN, 359
 McCann, 21, 35, 94, 251, 257, 260, 268, 274, 275, 279, 280, 281, 283, 291, 344, 376, 377, 387, 389, 394, 412
 McCarrison, 291
 McClellan, 262
 McClure, 367
 McConnell, 156
 McCrudden, 166, 199
 McKinlay, 345
 MacCallum, 368
 Macleod, G., 138, 146, 150, 151, 162, 180
 Macleod, J. J. R., 278
 Magnus-Levy, 20, 48, 49, 72, 90, 130, 133, 138, 153, 217, 232, 242, 251, 255, 264, 291, 292, 310, 316, 318, 356, 407
 Mandel, 253, 254
 Marine, 287, 288, 318
 Marsh, 135, 182, 262
 Mason, E. H., 158, 240, 247, 252, 272, 276, 328
 Mason, H., 158
 Mattill, 210
 Maurer, 366, 413
 Mayer, 156, 410
 Meakins, 315

Means, 168, 175, 176, 204, 231, 239,
264, 294, 310, 312, 314, 324, 326,
328, 330, 343, 355, 358, 359, 360,
412, 413

Meeh, 112, 231

Melcher, 126

Merrill, 324

Meyer, 355, 356, 362, 364

Meyerhof, 258

Michaelis, 72

Miescher, 213

Miles, 31, 179, 219, 245, 382

Milner, 88, 405

Minkowski, 253, 254

Minot, 306, 314, 360, 361

Mitchell, 198

Moebius, 291

Mohr, 244, 264, 276, 355

Möller, 180, 291, 303

Montoro, 161

Morgulis, 208, 217

Moriarty, 134, 208, 215, 300, 323, 407

Mortimer, 352

Mosenthal, 264

Mosse, 361

Moulton, 190, 196

Mueller, 208

Muirhead, 343

Mukerjee, 162

Müller, 17, 35, 292

Munk, 208

Murlin, 18, 21, 76, 106, 115, 134, 135,

137, 138, 182, 193, 202, 226, 278,

312, 351, 352

Murphy, J. A., 355, 358

Murphy, W. P., 279

Murschauser, 107

N

NEHRING, 232, 276, 292, 356

Nelson, 226

Neuwirth, 26

Newburgh, 262, 316

Nicholls, 279

Nobel, 316

Nolan, 254

Noorden, von, 230, 232, 276

O

OLESON, 226, 409

Olin, 139

Olmstead, 138, 139, 184

Osterberg, 26

Ott, 368, 369

Ozorio de Almeida, 160

P

PADDOCK, 311

Palmer, 263, 268

Paton, 213

Peabody, 65, 152, 197, 264, 305, 362,

364, 311

Peckham, 367

Peemöller, 158

Pemberton, 367

Perlzweig, 257, 260, 268

Peters, 60

Pettenkofer, 20, 79, 242, 356

Pettersson, 78

Pfaundler, 114, 123

Pirquet, von, 197

Plant, 413

Plaut, 158, 180, 223, 233, 345, 348

Plummer, 288, 289, 291, 323, 327, 414

Pollitzer, 47, 233

Porges, 292, 310

Porter, 330

Poulton, 222

Pribram, 292, 310

R

RABE, 223

Ragsdale, 147, 188

Rameaux, 194

Rapport, 31

Rasmussen, 102

Ray, 126, 196

Read, 314, 326, 328

Regnault, 18, 90, 194

Reilly, 254

Reiset, 18, 90, 194

Richardson, E. P., 330, 332

Richardson, H. B., 46, 247, 252, 259,

268, 272, 276, 277, 379, 401

Riche, 68, 76, 82, 292, 318

Richet, 19, 194

Richter, 368

Riethus, 391

Ringer, 25, 26, 30

Rivkin, 215, 268

Robin, 242

Rolland, 375

Rolly, 45, 97, 233, 239, 243, 273, 371,

391, 393

Ronchi, 113
 Root, H. F., 179, 278, 352
 Root, H. K., 352
 Rosa, 81
 Rose, 150, 180
 Rosenfeld, 262
 Rosiewitz, 97
 Ross, 208, 211
 Roth, 31, 99, 170, 219, 245, 273
 Roussy, 115, 123
 Rowe, 349, 352
 Rowntree, 216, 344, 349, 398, 414
 Rubner, 24, 28, 29, 35, 81, 169, 194,
 195, 195, 216, 247, 399
 Rudinger, 309
 Ryffel, 222

S

SALOMON, 239, 277, 292
 Sanborn, 179
 Sandiford, I., 21, 76, 94, 118, 125,
 126, 148, 177, 205, 226, 232, 254,
 273, 279, 282, 289, 295, 297, 308,
 318, 340, 343, 344, 351, 354, 357,
 359
 Sandiford, R. B., 120, 284
 Sands, 315
 Sanger, 306, 310, 359
 Sansum, 377, 404
 Sarrus, 194
 Saunders, 233
 Sawyer, 115, 292
 Schadow, 102
 Schick, 316, 371
 Schill, 408
 Schlossmann, 107
 Schmidt, 194
 Schmoll, 242, 276
 Schneider, 159
 Schoendorf, 25
 Schumberg, 28, 38, 39, 71
 Schwenkenbecker, 400
 Segall, 328, 330
 Seguin, 159, 208
 Senator, 208
 Shaffer, 36, 215, 250, 262, 263, 264,
 268, 270, 280, 371, 372
 Shaw, 208, 215
 Sicheff, 113
 Siebert, 366
 Sisson, 134
 Sívén, 34
 Smith, H. M., 31, 163, 219, 245
 Smith, M., 35

Snell, 344, 349, 414
 Soderstrom, 52, 82, 292, 310, 400
 Sonden, 78, 139, 153
 Speck, 409
 Stähelin, 239
 Stander, 367
 Starr, 328, 330
 Stern, 331, 342
 Stevenin, 345
 Steyrer, 292
 Stiles, 254
 Stolz, 47, 233
 Stone, 115, 292
 Stoner, 121, 173, 178, 179
 Straub, 216
 Strauss, 355
 Stroman, 407
 Strouse, 230, 232, 233
 Sturgis, 303, 305, 311, 314, 336, 340,
 343, 389
 Stuve, 232, 292
 Succi, 215
 Sutliff, 190, 312
 Svenson, 217, 232, 233, 292, 370, 391

T

TAKAHIRA, 121, 150, 161, 168, 180,
 208, 223
 Talbot, 21, 107, 125, 134, 136, 137,
 138, 139, 147, 154, 164, 182, 200,
 201, 208, 215, 225, 302, 323, 345,
 407
 Taylor, 319
 Terroine, 198
 Theodor, 354
 Thiele, 232, 292, 356
 Thomas, 35, 36, 45
 Tierney, 344, 348
 Tigerstedt, 139, 153, 368
 Tileston, 230
 Tillotson, 406
 Timm, 348
 Tisdale, 208, 211
 Tissot, 92
 Tompkins, 89, 257, 260, 268, 293,
 305, 311, 314, 355, 356, 367
 Torrey, 396
 Traumann, 408, 410
 Truesdell, 159

U

UNDEUTSCH, 292, 310
 Uridil, 319

V

VAN BOGAERT, 345
 van't Hoff, 390
 Van Slyke, 366
 Veeder, 80, 242
 Voit, 20, 31, 195, 242, 356
 von Bergmann, 239, 292
 von Glahn, 413
 von Leyden, 371
 von Noorden, 230, 232, 276
 von Pirquet, 197
 von Willbrand, 158, 232, 401

W

WAGNER, 103, 237
 Wakeham, 349
 Walker, 126, 196
 Wang, 227, 232, 233
 Watson, 53
 Wearn, 305, 311
 Wechselmann, 401
 Weintraub, 242
 Weiss, 61
 Wentworth, F. W., 197
 Wentworth, J. A., 367
 West, 197
 Wheeler, 354
 Whitehorn, 406

Wilder, 244, 248, 251, 254, 261, 270,
 274, 275, 278, 280, 282
 Willebrand, von, 158, 232, 401
 Williams, 82
 Willius, 363
 Wilson, C. M., 114
 Wilson, D., 114
 Wilson, J. R., 90, 108, 215, 268
 Wilson, L. B., 291
 Wilson, R. E., 102
 Wiltshire, 350
 Winter, 251, 270
 Wislicenus, 36
 Wolpert, 400
 Woodwell, 175, 176, 204
 Woodyatt, 245, 262, 264, 280, 377,
 404
 Wörner, 121
 Wright, 268

Y

YAGLOGOU, 156

Z

ZELLER, 262
 Ziegler, 411
 Zuntz, 28, 38, 39, 71, 158, 198, 208,
 218, 251, 348, 349, 351

SUBJECT INDEX.

A

ABSORPTION of food. *See* Food.
 Acetaldehyde, 49
 Acetonitril, 312
 Acetonuria. *See* Ketosis.
 Acetyl-salicylic acid, 413
 Acidosis. *See* Ketosis.
 Acromegaly, 297, 299, 345
 Addison's disease, 297, 299, 343
 Adenomas. *See* Thyroid.
 Adrenalin. *See* Epinephrin.
 Adrenals. *See* Epinephrin.
 Adults, metabolism of, 145, 148
 Age, effect of, 138, 145, 148, 188
 in diabetes, 248
 Air, alveolar, 59, 64
 analysis, 78
 complemental, 60
 composition of, 59
 expired, 59
 supplemental, 60
 temperature of, influence on
 metabolism, 131
 tidal, 59
 Alcohol, 412
 checks, 89, 105
 Allen treatment in diabetes, 279
 Altitude, 158
 Amino-acids, 32, 48
 Anemia, 64, 297, 299, 355, 400
 Animals, metabolism of, 194, 212
 Antiketogenic substances, 214
 Appetite, regulation of food-intake
 by, 229
 Arthritis, 267, 297, 299
 Asthenia, 297, 299
 Athletic training, 163
 Atropine, 311, 413
 Atwater - Rosa - Benedict respiration
 calorimeter, frontispiece, 81
 Aub and Du Bois, standards of basal
 metabolism, 169, 199, 200
 Auspumpung, 60, 68, 409
 Autonomic imbalance, 301
 Avogadro's law, 54

B

BAILEY, standards of normal, 149
 Bardeen, height-weight index of, 126
 Basal metabolic rate. *See* Metabo-
 lism, basal.
 Basedow's disease. *See* Goiter, ex-
 ophthalmic.
 Benedict, respiration apparatus of,
 89, 94, 97, 107
 and Benedict, student respira-
 tion apparatus of, 102
 and Collins, respiration appara-
 tus of, 99
 -Roth respiration apparatus, 100
 -Sanborn apparatus, 99
 standards for children, 183
 surface area, photographic meth-
 od of determining, 122
 Beta-oxybutyric acid, 256
 Blood, diseases of, 247, 355
 -pressure, high, 364
 sugar, 25
 in thyroid disease, 306
 Body, composition of, 190, 196, 211
 -surface. *See* Surface area.
 Boothby and Sandiford, nomograms,
 120, 284
 Boothby's table of basal metabolic
 rate in disease, 296-299
 Boy Scouts, metabolism of, 142
 Boyle's law, 53, 57
 Bouchard, surface-area formula of,
 113
 Brazilians, metabolism of, 134
 Breakfast, effect of, 52

C

CAFFEIN, 412
 Caisson disease, 65
 Calcium phosphate in diabetes, 275
 Calories, 76
 percentage of, from protein, etc.,
 74

- Calorific value of oxygen, 23, 30, 69, 72
 Calorimeter, 75
 Atwater-Rosa Benedict, frontis-piece, 81
 bomb, 76
 dog, 81
 Calorimetry, air analysis in, 78
 direct, 67, 76
 indirect, 67, 70
 Camphor, 413
 Capacity. *See* Vital.
 Carbohydrate, 22, 41, 46
 conversion of, into fat, 30, 44
 diet and body weight, 405
 effect of ingestion, 48
 in fasting men, 25, 211
 from fat, 31
 from protein, 44, 254
 oxidation in diabetes during fasting, 258
 storage of, 211, 259
 Carbohydrates, effect of various, in diabetes, 272
 metabolism of, 22
 Carbon dioxide and auspumpung, 61, 68, 409
 breathing of, 65
 grams to liters, 22, 57
 as index of atmospheric contamination, 65
 as measure of metabolism, 67
 in submarines, 65
 Carbon-monoxide poisoning, 64
 Cardiac disease, 297, 299, 362
 Carpenter air-analysis apparatus, 78
 Castration, 348
 Catamenia. *See* Menstruation.
 Cattle, composition of, 196
 Chamber, cot respiration, 89
 Charles's law, 53
 Chemical regulation of metabolism, 155
 Children, Benedict standards, 183
 height-weight relationship of, 127
 metabolism of, 106, 133-148
 surface area of, 123
 Chills, 369, 378
 Chloride, in fever, 393
 Chlorosis, 355
 Cholera, 395
 Cholesterol, 310
 Climate, 154
 Coma, diabetic, 247, 284
 Convalescence, metabolism in, 217, 370
 Cooling of body, 186, 193
 Cost of digestion, 50
 Cot chamber, 89
 Cretinism, 290, 301
- ## D
- D:N. *See* Dextrose to nitrogen ratio.
 Dalton's laws, 54
 Dead body, loss of heat of, 186
 space, 59
 Dementia precox, 406
 Dermatological disease, 297, 299
 Dextrose. *See* Glucose.
 to nitrogen (D:N) ratio, 44, 252
 Diabetes, 241-286, 297, 299
 and D:N ratio, 252
 calculation of respiration experiments in, 255
 coma, metabolism in, 247, 284
 diet in, 279
 exercise in, 276
 fasting, effect of, in, 243
 food, effect of, in, 272
 insipidus, 346
 insulin, effect of, on respiratory quotient in, 246, 277
 ketosis in, 244, 262
 metabolism in, 241
 nitrogen excretion in, 260
 protein destruction in, 244, 247, 260
 respiratory quotient in, 249
 specific dynamic action in, 247
 storage of carbohydrate in, 259
 treatment of, 241, 279
 water vaporization in, 400
 Diagnosis and basal metabolism, 303
 Diet in diabetes, 279
 in fever, 374, 395
 and food metabolized, 46
 influence on metabolism, 159
 Digestion, cost of, 50
 Douglas respiration apparatus, 94
 Dreyer formula, 173
 Drugs, 412
 Du Bois, D., surface area, method of determining, 114-124
 Du Bois and Aub, standards of basal metabolism, 169, 199, 200
 Dwarfs, metabolism of, 167, 169
 after protein meal, 33

Dynamic action. *See* Specific Dynamic Action.
 Dysphagia, 297, 299
 Dyspnea, 362
 Dysthyroidism *versus* hyperthyroidism, 316
 Dystrophia adiposo-genitalis, 238

E

EDEMA and water vaporized, 400
 Emotions, 409
 Encephalitis lethargica, 297, 299
 Endogenous obesity. *See* Obesity.
 Enemata, 47
 Energy, conservation of, 56
 Environment, 158
 Epilepsy, 297, 299, 407
 Epinéphrin, 279, 343
 in exophthalmic goiter, 318
 Equimolecular ratio, 265, 280
 Erythemia, 297, 361
 Evaporation. *See* Water.
 Exercise in diabetes, 276
 Exophthalmic goiter. *See* Goiter, exophthalmic.

F

FA/G. *See* Fatty acid-glucose ratio.
 Fasting, 43, 208
 in diabetes, 271
 Fat, absorption of, 28, 29
 caloric value of, 28, 29
 composition of, 235
 diet and body weight, 403
 digestion of, 27
 formation of, from carbohydrate, 30
 metabolism of, 26
 respiratory quotient of, 29
 source of beta-oxybutyric acid, 255
 specific dynamic action of, 48
 storage of, 228
 in diabetes, 272
 in fever, 374
 water from oxidation of, 30, 216
 Fatty acid-glucose ratio, 265, 280
 tissue, analysis of, 235
 Feces, losses in, 52
 Fetal life, metabolism of, 134
 Fetus, surface area of, 125
 Fever, 368. *See* Temperature.

Fever from dehydration, 377
 diet in, 374, 395
 metabolism in, 388
 nursing in, 397
 water vaporization in, 400
 Food. *See* Diet.
 absorption of, 28
 in fever, 373
 effect of, on metabolism, 46
 in diabetes, 272
 Foodstuffs, mixture of, 41
 Frölich's disease, 238

G

G:N. *See* Dextrose to nitrogen ratio.
 Gases of the body, 57
 properties of, 53, 57
 Gastro-intestinal disease, 297, 299
 Gay-Lussac's law, 53
 Glucose, 24
 from fat, 257
 from protein, 40, 254
 Glycerol, conversion of, into carbohydrate, 31, 257
 in diabetes, 275
 Glycogen, loss of, during starvation, 25, 211
 storage of, 25, 211
 in diabetes, 259
 in hyperthyroidism, 307
 in new-born, 137
 Goetsch test, 311
 Goiter. *See* Thyroid.
 colloid, 288
 exophthalmic, 289
 fasting in, 307
 food requirement in, 308, 338
 illustrative cases, 333
 muscular efficiency in, 308
 protein metabolism in, 306
 and pulse-rate, 312
 specific dynamic action in, 310
 theories of causation, 316
 treatment of, 323
 Gonads, 292
 Gout, 367
 Graves' disease. *See* Goiter, exophthalmic.
 Growth, effect of, on metabolism, 188, 191
 Grundumsatz, 128
 Gynecological disease, 297, 299

H

- HALDANE apparatus, 78
 Handy model respiration apparatus, 100
 Hannon and McCann diet in diabetes, 282
 Harris-Benedict, multiple prediction formula, 170, 204
 normal standards of basal metabolism, 171
 Heart-block and effect of thyroid extract, 342
 disease, 297, 362
 water vaporization in, 400
 Heat. *See* Temperature.
 of combustion, 55
 loss, rate of, in body, 186
 measurement of, 76
 physical laws of, 54
 specific, of body, 382
 Height, 203
 Height-weight chart, 119-124
 relationship, 126
 Hemochromatosis, 197
 Henderson apparatus, 78
 Heroin, 413
 Hexose-phosphate in diabetes, 275
 Hodgkin's disease, 297
 Humidity and water elimination, 399
 Hydrothermal equivalent, 76, 87
 Hypertension, essential, 297, 299, 364
 Hyperthyroidism. *See* Goiter, exophthalmic.
 from thyroid overdosage, 342
 versus dysthyroidism, 316
 Hypnosis, 408, 410
 Hypophyseal disease, 344
 Hypothyroidism. *See* Myxedema and Cretinism.
 basal metabolism in, 300

I

- ICTHYOSIS hystrix, 401
 Inanition, chronic, 217
 Infants, 137
 Insanity, 406
 Insulin, effect of, in diabetes, 246, 277
 Interstitial glands. *See* Sex glands.
 Iodine and thyroid disease, 327, 414
 Iodothyrim, 322
 Iodo-thyro-globulin, 322

J

- JONES respiration apparatus, 100
 Joule heat equivalent of work, 55

K

- KATONIC, stupor, 407
 Ketogenic-antiketogenic ratio, 263, 265, 280
 Ketosis, 44
 in children, 268
 in diabetes, 244, 248, 262
 and respiratory quotient, 256, 269
 severe, 264
 in starvation, 214
 threshold of, 263, 268
 Kidney disease, 297, 299, 364
 water vaporization in, 400
 Krogh respiration apparatus, 102
 standard metabolism of, 128, 145, 151, 175

L

- LANGWORTHY and Milner respiration calorimeter, 88
 Legless men, metabolism of, 169
 Levanzin's fast, 208
 Levulose in diabetes, 273
 Leukemia, 297, 299, 357
 Ligation, in exophthalmic goiter, 331
 Linear formula, 115-117
 Lissauer surface area formula, 113
 Liver, storage of glycogen in, 25
 Lugol's solution, 327, 414
 Lungs, water elimination from, 399
 Lusk, calculation of non-protein respiratory quotient, 39
 D:N ratio of phlorhizinized dogs, 253
 Luxus konsumption, 235
 Lympho-granulomatosis, 360

M

- MCCANN and Hannon, diet in diabetes, 282
 Malarial chills, 378
 imitation of, 378
 Malignant disease, 297, 299
 Meeh's formula, 112

- Menopause, 348
 Menstruation and metabolism, 340, 349
 Mental activity, 408
 disease, 297, 299, 406
 Metabolism and age, 138, 148, 188
 after enemata, 42
 food, 32, 33, 43, 46, 50, 162
 basal, in adult life, 145, 148
 and altitude, 158
 and light, 158
 and puberty, 139, 147
 and race, 159
 Aub and Du Bois curve, 199
 calculations, 67, 71
 and carbon dioxide, 68
 of children, 133-148, 182
 in disease, 249
 constancy, 128, 132
 definition of, 128
 during day, 131
 factors which influence, 128, 165
 of fetal life, 134
 management of tests for, 109
 of new-born, 136
 normal standards, 140, 145, 149, 151, 164, 169-175, 199, 200, 297, 299
 Aub and Du Bois standards, 169, 199
 Bailey standards, 149
 Dreyer's formula for, 173
 Harris-Benedict standards, 170, 204
 Krogh standards, 128, 145, 151, 175
 Sage standards, 166, 199
 post-absorptive, 128
 range of, 130, 147
 reliability of, 303
 uniformity of, 130, 195
 variations in, 130, 147, 304
 in various diseases not due to thyroid, 297, 299
 of women, 153
 history of, 17
 of normal women during diabetic treatment, 246
 theories concerning, 186
 total, 46, 51, 69
 zones of, 44
- Methane, 66
 Michaelis calculation of caloric value of oxygen, 72-74
 Migraine, 297, 299
 Mixtures metabolized, 41
 Mongolian idiot, 302
 Morphine, 413
 Murlin respiration apparatus for infants, 108
 Muscle tonus and metabolism, 192, 407
 Muscular efficiency in disease, 309
 in obesity, 235
 during undernutrition, 222
 exercise, 46
 Myxedema. *See* Hypothyroidism.
- N
- NEGROES, 160
 Nephritis, 364
 Nephrosis, 366
 Nervous exhaustion, 297, 299
 system, 406
 Neurasthenia, 297, 299
 New-born, 136
 Newton's law of cooling, 55, 193
 Nitrogen. *See* Protein, 31-52.
 balance, 35
 in diabetes, 247, 252
 in exophthalmic goiter, 306, 335
 in fasting, 209
 in feces, 36
 gas, in blood, 65
 in respiration experiments, 66
 in metabolism calculations, 70-74
 minimum, 45, 223
 in exophthalmic goiter, 309
 in fever, 36, 372
 in leukemia, 360
 in pneumonia, 393
 in syphilis, 395
 in pneumonia, 392
 in sputum, 393
 in typhoid fever, 36, 371
 in undernutrition, 209, 212
 wear and tear quota, 35
 Nomograms of height-weight formula, 120, 124
 Non-protein R. Q., 39
 Normal standards. *See* Metabolism.
 Nursing in fever, 397

O

- OBESITY, 168, 203, 228, 297, 299
 constitutional, 238
 endogenous, 238
 simple or exogenous, 229
 specific dynamic action in, 233
 and water storage, 405
 Occupation and metabolism, 163
 Old age, 152
 Orange juice in diabetes, 274
 Oranges, composition of, 274
 Orientals, 159
 Orsat apparatus, 77, 78
 Overnutrition, 168, 203, 228
 and *Luxus Konsumption*, 235
 Oxycalorimeter, 77
 Oxygen, calorific value of, 23, 28, 39,
 69, 73
 when fat is formed from car-
 bohydrate, 30
 effect of, on metabolism, 64, 159,
 414
 grams to liters, 22, 57

P

- PAGET's disease, 297, 299
 Paralyzes, metabolism in, 406
 Paralysis agitans, 407
 Percentage of calories, 39, 42, 74
 Pernicious anemia. *See* Anemia.
 Pettenkofer and Voit chamber, 19,
 68, 79
 Phlorhizin diabetes, 252
 specific dynamic action in, 48
 Phosphates in diabetes, 275
 Physical regulation of metabolism,
 155
 Physics, laws of, 53, 381
 Pituitary disease, 297, 299, 344
 Plethora of carbohydrate, 49
 Pneumonia, 391
 Polycythemia, 297, 361
 Postabsorptive metabolism, 128
 Pregnancy, 297, 299, 351
 Prematurity, 134
 Protein. *See* Nitrogen, 31-52
 in diabetes, 247, 252, 260
 in exophthalmic goiter, 306, 335
 in fasting, 209
 in feces, 36
 foreign, and chill, 280
 in leukemia, 360
 metabolism, calculation of, 36,
 37, 70-74

- Protein minimum, 36, 45, 223, 309,
 372, 393, 395
 percentage of calories from, 70-
 74, 261
 in pneumonia, 392
 in syphilis, 395
 toxic destruction of, 36, 371
 in typhoid fever, 36, 371
 in undernutrition, 209, 212
 water from oxidation of, 31, 216
 wear and tear quota. *See* Mini-
 mum.
 Protoplasmic mass, 190, 196, 198
 Puberty, metabolism at, 139, 147
 Pulse pressure and basal metabolism,
 314
 Pulse-rate, 192
 and basal metabolism, 190,
 192, 312
 during fast, 209
 in hyperthyroidism, 312
 in leukemia, 315, 360
 in undernutrition, 220

Q

- QUININE, effect of, on basal metabo-
 lism, 413
 Quotient. *See* Respiratory quotient.

R

- R. Q. *See* respiratory quotient.
 Race, influence of, on metabolism,
 159
 Radiation, 55
 Radiotherapy. *See* Roentgen-ray.
 Radium treatment of exophthalmic
 goiter, 327
 in leukemia, 358
 Re-alimentation, 223
 Regnault and Reiset closed-circuit
 apparatus, 18
 Reliability, 303
 Respiration apparatus, 67, 75, 79
 Atwater-Rosa-Benedict cal-
 orimeter, frontispiece, 81
 Benedict portable, 97
 and Benedict student,
 102
 and Collins, 99
 -Roth, 100
 -Sanborn, 99
 universal, 94

- Respiration apparatus for carbon dioxide, 103
 for children, 106
 of Douglas, 94
 of Hagedorn, 105
 of Jones, 100
 of Krogh, 102
 McKesson metabor, 99
 Sanborn handy model, 100
 Schlossman and Murschauser, 107
 selection of, 108
 of Tissot, 92
 of Zuntz and Geppert, 90
 physiology of, 57-66
 Respiratory metabolism. *See* Metabolism.
 quotient, 23, 39
 after food, 32
 after meat, 32
 after sugar, 273
 and caloric value of oxygen, 73
 and insulin, 278
 and ketosis, 264, 269
 on carbohydrate-free diet, 251
 in diabetes, 249, 255, 269, 276
 effect of auspumping on, 61
 in fever, 370, 374
 for fat, 29
 high, 252
 in hyperthyroidism, 307
 low, 62, 250
 after carbohydrate ingestion, 273
 of new-born, 137
 non-protein, 38, 39, 72-79, 251
 of protein, 37
 total, 41-46, 72-74
 when fat is formed from carbohydrate, 30
 Rest, in exophthalmic goiter, 323
 Rheumatic fever, 395
 Riche bomb calorimeter, 76
 Richet surface area law, 19, 194
 Roentgen-ray treatment in leukemia, 358
 in thyroid disease, 324
 Rolly and Rosiewicz modification of Benedict respiration apparatus, 97
 Roussy surface area, methods of determining, 115, 123
 Rubner respiration calorimeter, 19, 81
 surface area law, 19, 194
 Russell Sage Institute of Pathology, respiration calorimeter, frontispiece, 82
 standards, 169, 199, 200
 surface area, the method of determining, 114-124
- S**
- SAGE. *See* Russell Sage.
 metabolism curve, 199
 standards of metabolism, 169, 199, 200
 Salmon during spawning, 213
 Sanborn respiration apparatus, 99
 Sarcoma, Kundra's, 360
 Scarlet fever, 395
 Schlossmann and Murschauser respiration apparatus for infants, 107
 Scouts, metabolism of, 139
 Sex, in diabetes, 249
 expression of, during undernutrition, 222
 glands, 292
 influence of, on metabolism, 153, 347
 Shaffer's ratio, molecular, 263, 270
 Shivering, 155, 369, 378
 Short men, 203
 Sicheff surface area, 113
 Skin disease, 297, 299
 Sleep, influence of, on metabolism, 164
 Small breakfast, effect of, on metabolism, 50, 52
 Soda-lime, preparation of, 78
 Sodium salicylate, 413
 Sonden-Pettersson air-analysis apparatus, 78
 Specific dynamic action of carbohydrate, 48
 in diabetes, 247, 272, 275
 in disease, 47
 in exophthalmic goiter, 310
 of fat, 48
 in fevers, 371, 374, 394
 in obesity, 233

- Specific dynamic action in pituitary disease, 345
 of protein, 32, 33, 46
 heat, 54
 of body, 87, 382
 Sputum, nitrogen of, 393
 Standard metabolism, 128, 145, 151, 175
 Starch, 22
 Starvation, 43, 208. *See* Fasting and Undernutrition.
 Stefan's laws of radiation, 55
 Strychnine, 413
 Student respiration apparatus, 102
 Sugar and respiratory quotient, 273
 Sugars in diabetes, effect of, 273
 "Suit of clothes" action of skin, 156, 193, 199, 386
 Sulphur from protein, 33
 Surface area, Bardeen's method, 126
 and basal metabolism, 18, 167, 193-206, 230
 Benedict's photographic method, 122
 of children, 123
 Du Bois method, 114-124
 estimation of, 112
 of fetus, 125
 height-weight formula, 118-124
 Meeh's formula for, 112
 and obesity, 230
 Roussy's method, 115, 123
 Surplus cellular nitrogen, 31
 Sweating, 381, 401
 Syphilis, nitrogen minimum in, 395
- Thyroid disease, and carbohydrate metabolism, 306
 classification of, 287
 diagnosis of, 303
 drugs in, 311
 iodides in, 414
 malignant of, 291
 protein in, 308
 review of literature of, 291
 treatment of, 319
 water of vaporization in, 310
 extract, 321
 function in *luxus konsumption*, 237
 in obesity, 238
 Thyroidectomy, 331
 Thyroidine, 322
 Thyrotoxicosis. *See* Goiter, exophthalmic.
 Thyroxin, 319, 322
 Tissot respiration apparatus, 92
 Tonsillitis in goiter patient, 339
 Tonus, muscle, 192, 407
 Toxic adenoma, 289
 destruction of protein, 36, 371
 Transfusion in anemia, 357
 Tremors, 407
 Triangles to represent metabolism, 41-45, 73, 74
 Tripalmitin oxidation calculation, 28
 Tropics, 159
 Tuberculosis, 377, 393
 Typhoid fever, 373
 diet in, 375
 vaccine, intravenous, producing chill, 380

T

- TABES, 297, 299
 Talbot, metabolism of children, normal standards, 140
 Tall men, 203
 Temperature. *See* Fever and Heat.
 of air and water elimination, 399
 body, 382
 during fast, 210
 coefficients, 390
 high, from water loss, 377, 404
 influence of, 154
 and level of metabolism, 339
 regulation, 368, 377, 385
 Thin men and women, 168, 203
 Thyroid, adenomas of, 287
 disease, 292-306

U

- UNDERNUTRITION, 168, 203, 207, 297, 299
 chronic, 217
 muscular efficiency during, 222
 of Y. M. C. A. students, 219
 Unit respiration apparatus, 94
 Universal respiration apparatus, 94
 Uremia, 366
 Urethane anesthesia, 319

V

- VAN'T HOFF's law, 389
 Vaporization. *See* Water.
 heat of, 56

Vegetarians, 162
Ventilation of lungs, 60
Vital capacity, 60, 197, 363

W

WATER, 216, 398
 in fever diet, 397
 in foods, 398
 from oxidation of fat, protein
 and carbohydrate, 24, 29, 216
 starvation, 216
 vaporization during fasting, 210
 in health and disease, 400
 in leukemia, 358
 in thyroid disease, 310
Wear and tear quota of nitrogen, 35.
 See Nitrogen minimum.
Weight, body, 228, 238, 398, 403
 during fasting, 210
 undernutrition, 219
 and metabolism, 167, 203

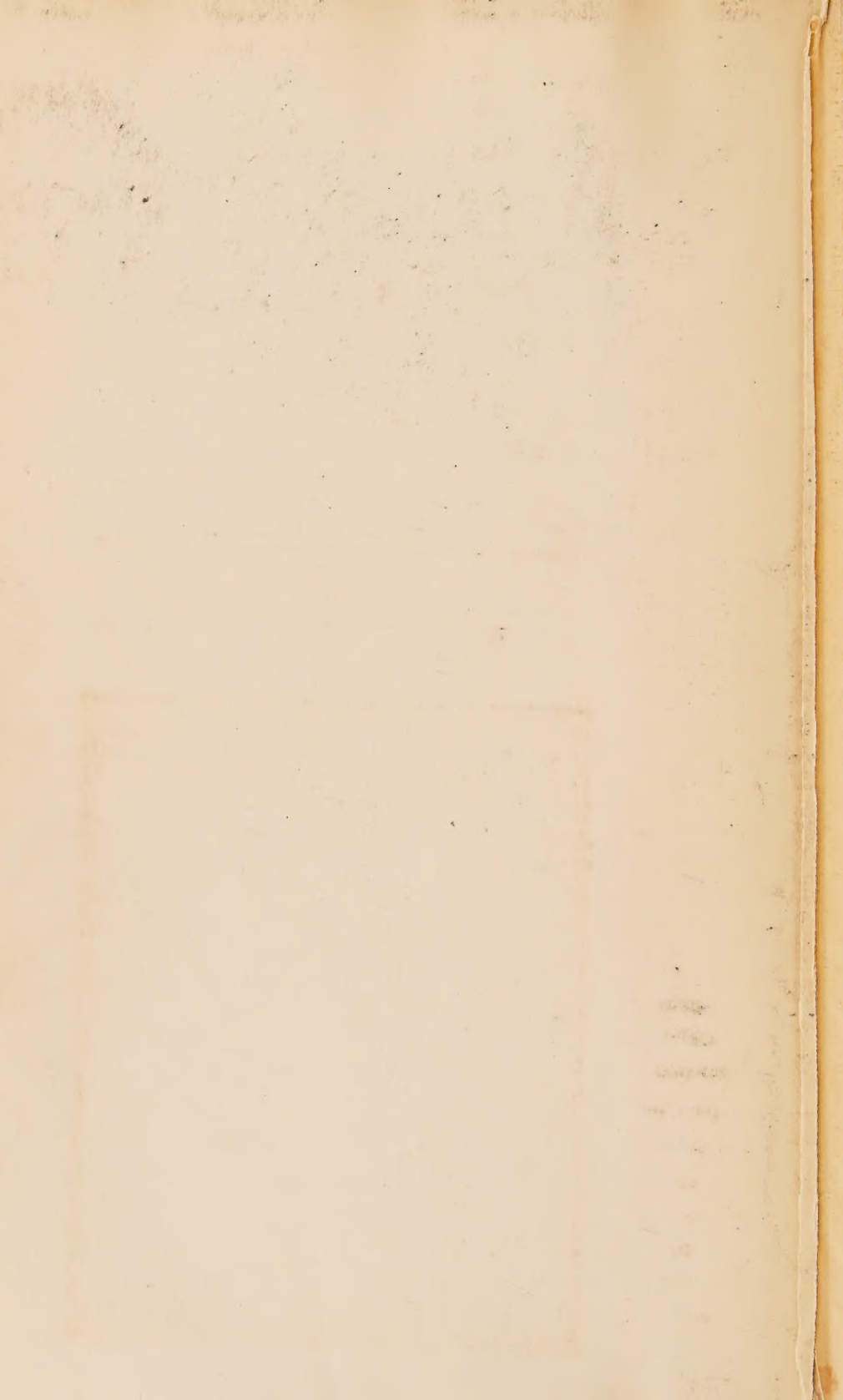
Wilder diet in diabetes, 282
 nomogram for, 284, 285
Women, metabolism of, 153, 246, 347
Woodyatt diet in diabetes, 280
 ketogenic-antiketogenic formula,
 264
Work, heat equivalent of, 55
 and respiratory quotient, 61

X

X-RAY. *See* Roentgen-ray.

Z

ZIMMERRUHE, metabolism during, 80
Zones of metabolism, 44
Zuntz-Geppert respiration apparatus,
 19, 90
 and Schumburg table, 39, 71-74



3 8482 00150 3347

QP171 .D72

DuBois, E. F.

QP171

.D72

MELLOR INSTITUTE,
PITTSBURGH, PA.



3 8482 00150 3347

Carnegie Mellon Offsite Facility



A106353